American Heart Journal

VOL. 25 MAY, 1943 NO. 5

Original Communications

PULMONARY EMBOLISM WITH AND WITHOUT ACUTE COR PULMONALE, WITH ESPECIAL REFERENCE TO THE ELECTROCARDIOGRAM

DONAL MURNAGHAN,* M.B., B.CH., SYLVESTER MCGINN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

PULMONARY embolism, always a common condition, has only in recent years begun to attract as much attention on the part of internists as it deserves. Surgeons and obstetricians have been more or less aware of thrombophlebitis and pulmonary embolism as complications of operations and childbirth for generations, but physicians at large have not been cognizant of the large role that peripheral (especially in the leg) thrombophlebitis and pulmonary embolism play in complicating or simulating either acute or chronic illness of a medical nature. Now that a healthy change in viewpoint is beginning, it is imperative that there be a clear recognition of the most important symptoms and signs of these conditions. There tend to be, for example, in thrombophlebitis a slight degree of fever and leucocytosis and an increase in the sedimentation rate, even though there may be very little objective evidence on physical examination prior to the occurrence of pulmonary embolism. And in the case of pulmonary embolism itself, there are many suggestive symptoms and signs, including sudden dyspnea or oppression in the chest, tachycardia otherwise unexplained, fever, leucocytosis, râles in the lungs, even at both bases in the absence of congestive failure, and, relatively infrequently, the classical signs of extensive pulmonary consolidation, with or without pleuritis and hemoptysis.

One of the methods of study which has given positive results in some cases of pulmonary embolism is electrocardiography, but confusion exists in the literature as to its exact place in the diagnosis of the condition. It is our aim to help to clarify the situation by pointing out, first, that in the minority of cases the changes may be pathognomonic, second, that

Received for publication July 2, 1942.

*Traveling Student in Medicine, National University of Ireland, Research Fellow in Medicine, Harvard Medical School, Boston.

nondiagnostic changes may occur, as in the case of myocardial ischemia, particularly in the presence of important pre-existing coronary heart disease, and, third, that in many cases of pulmonary embolism one should not expect to find any electrocardiographic changes at all.

The literature contains several contributions on pulmonary embolism in which most of the emphasis has been placed on the electrocardiographic abnormalities. Not all the observers agree that constant variations do occur. Confusion has arisen because of the failure to make the distinction between those with, and those without, acute cor pulmonale. Barnes[1] pointed out that patients with the greatest circulatory embarrassment, together with features of shock, were the most likely to have the typical electrocardiographic changes. Love, Brugler, and Winslow[2] reported twelve cases of pulmonary embolism, of which seven showed all or most of the characteristic changes. Stewart, Kirk, and Smith[3] studied twelve cases of pulmonary embolism, in five of which the diagnosis was confirmed by post-mortem examination. These cases were selected from a larger group in which there were complicating factors which, by themselves, could modify the electrocardiogram. Their observations were essentially the same as those originally noted by McGinn and White[4] and those to be reported in this paper. Scherf and Schönbrunner[5] reported eight cases (no autopsies), in only one of which were there typical electrocardiographic changes. Sokolow, Katz, and Muscovitz[6] reported fifty unselected cases of pulmonary embolism, with twenty-seven autopsies, and reviewed the electrocardiographic observations. Five patients showed the changes described as occurring in acute cor pulmonale; of the remainder, nineteen had heart disease prior to the occurrence of the embolism, twenty-seven had electrocardiographic changes which, they said, may have antedated the embolism, and nine showed some of the characteristics of recent myocardial infarction in their electrocardiograms. They stressed the importance of putting the chest electrode over the right ventricle in order to obtain the typical inversion of the precordial T wave, which they attributed, as have we, to strain on that chamber. Horn, Dack, and Friedberg[7] studied forty-two cases of pulmonary embolism and found evidence of recent structural damage in the myocardium in eight cases. In these the embolism was recurrent, and several days had elapsed before death, allowing time, they considered, for such changes to occur. These authors believe that the myocardial changes were the result of ischemia, and that they accounted for the electrocardiographic variations. They suggest that diminished blood flow through the right coronary artery, caused by increased tension in the right ventricle, may explain the resemblance of the electrocardiographic changes in cases of pulmonary embolism to those in myocardial infarction of the posterior wall. Some of the hearts in which these changes were reported showed an increase in weight, muscle hypertrophy, and disease of the coronary arteries. Wood,[8] in presenting ten unselected cases of pulmonary embolism, pointed out the result of

different chest electrode positions on the precordial lead. He found that the T-wave inversion was (1) maximal and for the longest duration with the electrode in the right "pectoral" position, (2) usually present, but for a shorter time, when the electrode was in the left "pectoral" position,* and (3) rarely present, and for the shortest time, with the electrode over the apex of the heart. He placed the indifferent electrode on the right arm (the modern IV-R, or CR). Love, Brugler, and Winslow[2] produced pulmonary embolism in dogs experimentally, using clotted autogenous blood. They concluded that dilatation of the right ventricle was the significant factor in altering the electrocardiogram, and, furthermore, that myocardial anoxemia and reflexes through the vagus or sympathetic nerves played no important roles.

ACUTE COR PULMONALE IN PULMONARY EMBOLISM

The acute cor pulmonale was described by McGinn and White[4] as the result of sudden distention of the right ventricle and auricle which followed obstruction to the pulmonary circulation by an embolus. They observed that certain consistent variations from the normal appeared in the electrocardiograms of a number of patients with this condition.

Ten additional cases of acute cor pulmonale are now presented, with their electrocardiograms, to analyze further such changes as were noted in the original article. The cases were selected so that complicating heart disease and other factors which of themselves may modify the electrocardiogram were excluded. Five patients died, of which number three were examined post mortem; and five survived.

For comparison, the data on ninety-two other cases of pulmonary embolism, in forty-two of which the diagnosis was substantiated at autopsy, have been reviewed with particular reference to the electrocardiographic changes, and will be discussed later.

The typical variations which occurred in the electrocardiograms of the ten patients with acute cor pulmonale were (1) the presence of, or a tendency towards, right axis deviation, with a prominent S wave in Lead I (the S-T segment may be slightly depressed in this lead), (2) a depressed S-T take-off in Lead II, followed by a rising S-T segment and a low, upright, or diphasic T wave, (3) a moderately deep Q wave, slight convexity of the S-T segment, and an inverted T wave in Lead III,† and (4) a diphasic, or, more often, an inverted T wave in Lead IV. (Lead IV-F, as recommended by the American Heart Association, was used throughout this study.)

Although the signs and symptoms in cases of nonfatal pulmonary embolism with acute cor pulmonale are becoming better known, the condition is of sufficient importance to demand a brief review of them. The

*The "pectoral" position is halfway between the midsternal line and the midclavicular line; the exploring chest electrode was connected with the left leg wire.

†Slight elevation of the S-T take-off in Lead III was also observed in a few cases of acute cor pulmonale.

outstanding clinical feature is the sudden onset of dyspnea or oppressive anterior thoracic pain, with or without a feeling of faintness, accompanied by rapid, shallow respirations and tachycardia. The patient may show evidence of increased venous pressure, with cyanosis, distended neck veins, and an increased pulmonic second sound. If shock and collapse predominate, the patient becomes pale, cold, and clammy, shows a marked fall in blood pressure, and has a fast, thready pulse. Many patients at first present the signs of increased venous pressure, which are soon followed by a state of shock. They may closely simulate patients with acute coronary occlusion when seen in this condition. Later, with the pleuritis which usually accompanies a pulmonary infarct, there may be pain on breathing, in one side of the chest or the other, or in the back, or even in one shoulder if the diaphragmatic portion of the pleura is involved.

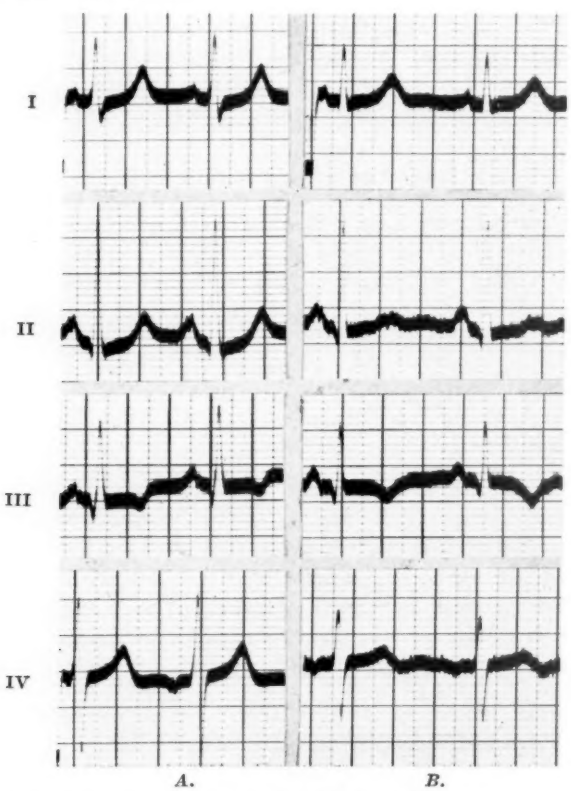


Fig. 1.—Case 1, M. D. P. *A*. February 23, 1940, three hours after first attack. *B*. February 26, 1940.

TEN NEW CASES OF ACUTE COR PULMONALE

CASE 1.—M. D. P., a 70-year-old woman, was admitted to the hospital February 10, 1940, with a dislocated left shoulder joint, complicated by a fracture of the great tuberosity of the humerus—the result of a fall the previous day. Reduction was carried out successfully under gas and oxygen anesthesia on February 11. Con-

valescence was uneventful until February 23, when the patient complained of a fainting spell, with substernal discomfort of sudden onset. She became very cyanotic and had difficulty in breathing. The pulse rate was 100, and the temperature was normal. Shortly after the onset, blood pressure was 90/50; within a few hours it rose to 110/70.

An electrocardiogram which was taken about three hours after the attack (Fig. 1-*A*) showed normal rhythm, a rate of 105, a short, but distinct, S wave in Lead I, and depression of the S-T segments in Lead I and Lead II. In Lead III a small Q wave was present, and the T wave was deeply inverted. The chest lead was normal. She improved rapidly with the aid of oxygen. A roentgenogram of the chest on February 26 showed haziness at the outer border of the left lung, below the scapula. An electrocardiogram on February 26 (Fig. 1-*B*) showed normal rhythm and a rate of 85. The S-T segments in Leads I and II had returned almost to the isoelectric line. The S waves in Lead I had practically vanished. A Q wave and a deeply inverted T wave were still present in Lead III. The T wave in Lead IV was low and slightly diphasic. On March 4, the patient suddenly collapsed, became ashen, cold, and clammy, and had a very weak pulse. The blood pressure was unobtainable. Marked air hunger and respiratory embarrassment were obvious, and she died in fifteen minutes.

At autopsy the heart weighed 350 grams; the right ventricular wall measured 4 mm., and the left, 14 mm., in thickness. The myocardium and the valves were normal. The right ventricle was slightly dilated, but the left was normal. Along the lateral portion and base of the left lung there was a wedge-shaped, red-brown infarct, 7 by 4 by 4 cm. A vessel proximal to it was occluded by a gray-red embolus. No other infarcts were seen, but ante-mortem emboli were scattered through the right lower lobe. The main pulmonary artery and its branches were occluded completely by a long, granular, coiled embolus. In the left popliteal vein, a red, granular thrombus similar to that in the pulmonary artery and its branches was present, and was partially adherent to the vessel wall. The left leg was slightly larger than the right.

Case 2.—W. R., a housewife, 40 years old and moderately obese, had injection treatment of varicose veins in both legs during 1937. In July, 1939, phlebitis occurred in the right leg, with thrombosis of the long saphenous vein, which became palpable up into the groin. A few days later she complained of a "chest cold," with right-sided neuralgia that was thought to be the result of sitting in a draft. On August 16, 1939, she experienced acute precordial pain which radiated to her left shoulder and was accompanied by rapid, shallow respirations. After this attack she found that it was extremely painful to breathe deeply, or to move around or roll over in bed. On August 17, physical examination showed that she was well nourished and moderately ill. There was a slight malar flush and her cervical veins were distended. The left border of cardiac dullness was 9 cm. from the midsternal line and 1 cm. outside the midclavicular line. The heart rate was 135. There were no murmurs. The pulmonic second sound was much accentuated, and louder than the aortic second sound. In the third and fourth left intercostal spaces, 1.5 cm. from the sternal margin, a rough, sticky sound (pleuro-pericardial friction rub?) was heard. The blood pressure was 150/90. The lungs and abdomen were negative on examination. In both legs thrombosed varicose veins were easily recognized.

An electrocardiogram (Fig. 2) taken on August 17 showed sinus tachycardia, a rate of 125, and a tendency toward low voltage of the QRS complexes. In Lead I an S wave was present, and the S-T take-off was depressed. In Lead II there was a gradual ascent of the S-T segment, and the T wave was flat. A prominent Q wave and deeply inverted T wave were present in Lead III. In Lead IV the R wave was small, and the T wave was very low. Early on the morning of August 18, the patient felt suddenly faint, but experienced no pain, and died shortly afterwards.

CASE 3.*—F. B., a 22-year-old single woman, was admitted to the hospital April 14, 1941. She had complained of intermittent pain in the right lower quadrant for two years. Physical examination was recorded as negative. An exploratory laparotomy was done on August 15 through a right rectus incision under spinal anesthesia. A mildly injected appendix and a small ovarian cyst were removed, and her immediate postoperative course was reported as satisfactory. She was nervous and restless on the third postoperative day, and had a temperature of 99° to 99.8° F., and a pulse rate of 90 to 100. No local cause was discovered which might explain the symptoms. Her appetite was not good during the subsequent three days. She was catheterized daily for the first five postoperative days, and during

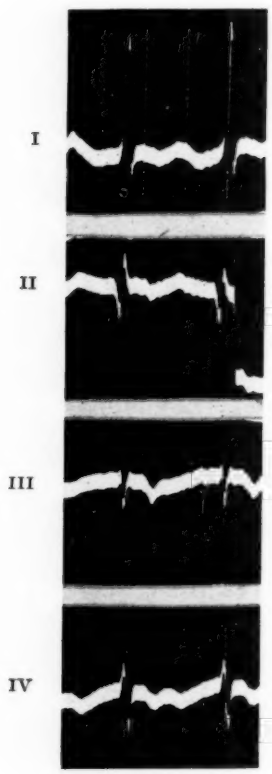


Fig. 2.

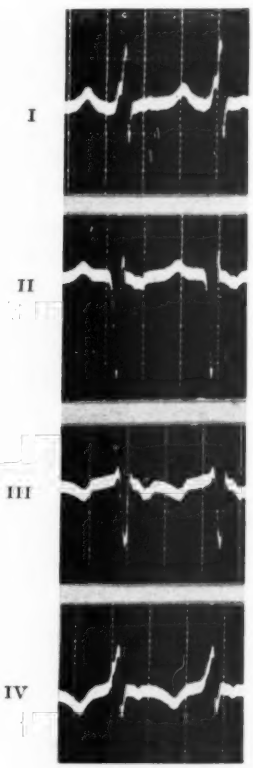


Fig. 3.

Fig. 2.—Case 2, W. R. August 17, 1939, 24 hours after most recent attack.
Fig. 3.—Case 3, F. B. April 24, 1941, 20 hours after first attack, 12 hours after second attack.

this time she developed a profuse vaginal discharge, with considerable pain. She "dangled" on the seventh day, and was out of bed walking in her room on the eighth postoperative day, April 23. That afternoon, while sitting in a chair, the patient complained of a "full" sensation in her chest and of feeling faint. Her face became cyanosed and she rapidly lost consciousness. Her respiration became rapid and stertorous, and no pulse could be felt. Oxygen and stimulants were applied, and the patient soon revived. Her pulse was noted as thready, weak and ir-

*Presented through the courtesy of Dr. Sherman Golden, Beverly, Massachusetts.

regular, with a rate of 120. She was cold and perspiring profusely, and her respirations were rapid, but quiet. During the night she again became cyanotic, pulseless, and complained of pain in her chest. Oxygen, stimulants, and digifolin were administered.

On April 24, twenty hours after the first attack, a consultant reported that she was ashen, apprehensive, and extremely weak. Her skin was cold and clammy. The temperature was 96.8°, the pulse rate, 120, and the respiratory rate, 35. Her blood pressure could not be obtained. The cervical veins were visible, but not engorged. Her heart was not enlarged. A systolic gallop was present over the precordium, and the pulmonary second sound was markedly accentuated and reduplicated. At the base of the left lung, in the posterior axillary region, the breath sounds were harsh, but no râles were heard. The edge of the liver was palpated two fingerbreadths below the right costal margin. There was no peripheral or dependent edema. The urine was normal; the leucocyte count was 18,000, with 81 per cent polymorphonuclears.

An electrocardiogram (Fig. 3), taken April 24, showed sinus tachycardia, a rate of 125, and well-marked right axis deviation. In Lead I there was a deep S wave, with moderate slurring of the upstroke of this wave. The S-T segment was slightly depressed in both Leads I and II. Lead III showed a Q wave and an inverted T wave. The T wave in Lead IV was inverted. The patient died one and one-half hours after the electrocardiogram was taken, and twenty-three hours after the onset of the first attack. Permission for post-mortem examination was not obtained.

CASE 4.—F. W. H., a 73-year-old man, developed a slight feverish cold on September 12, 1940, but was not incapacitated by it. He had an unproductive cough during the next two weeks. There was no history of chills, dyspnea, or chest pain. On October 7 he became feverish without observing any pain, and began to cough more than usual. Physical signs of consolidation of the right lower lobe were found on October 8 by his physician, who administered sulfapyridine. On October 11 he coughed up some bloodtinged sputum. When he was admitted to the hospital on the following day, physical examination showed an elderly man, perspiring and moderately cyanotic, with an emphysematous chest. There were moderate impairment of resonance and distinct bronchial breathing at the base of the right lung; generalized sonorous and sibilant râles were audible, and there were fine râles at the bases of both lungs. His temperature was 100°, his pulse rate, 80, and his blood pressure, 148/68. There had been no previous symptoms of heart disease, and examination of his heart on this occasion showed nothing remarkable. His leucocyte count was 20,000. The sputum was negative for 32 types of pneumococci. A "portable" roentgenogram of his chest, taken October 12, showed density at the right base suggestive of consolidation.

On October 23, an electrocardiogram (Fig. 4-*A*) showed normal rhythm and a rate of 120. There was a prominent S wave in Lead I, followed by a slight depression of the S-T segment. In Lead III there were a deep Q wave and a slightly inverted T wave. The T wave in Lead IV was upright, but low. A second "portable" roentgenogram, on October 22, showed mottled dullness in both lower lung fields that suggested a "bronchopneumonic process." On October 29, an electrocardiogram (Fig. 4-*B*) showed normal rhythm and a rate of 95. An S wave was still present in Lead I, but was less prominent than in the previous record. The Q wave was deep, and the T wave was definitely inverted in Lead III. The T wave in Lead IV was definitely lower than in the first tracing.

He improved during his stay in the hospital, and his leucocyte count fell to 11,000 by November 7. The physical signs in his chest diminished considerably. He was to return home on November 12, but complained of pain in his right leg which had troubled him a little in the previous two or three days. Phlebitis in the calf was suspected, for which he was treated conservatively. On November 15 he suffered a

sudden attack marked by extreme dyspnea and intense cyanosis, and died within a few minutes.

At post-mortem examination the heart weighed 425 grams. The right ventricular wall measured 4 mm., and the left, 12 mm., in thickness. The myocardium was firm and of normal color. The coronary arteries showed minimal sclerosis. There was no valvular disease. In the right ventricle a laminated, grayish, coiled thrombus lay twisted around the papillary muscles of the tricuspid valve. The pulmonary artery was distended with a pale, thrombotic mass similar to that which lay in the right ventricle; it penetrated into both main branches and into many of the smaller radicles, almost to the periphery of the lungs on each side, and more markedly in the upper than in the lower lobes. In the upper lobe of the right lung, adjacent to the interlobar septum peripherally, there was a small, brown infarct. In the posterior tibial veins of the right leg, approximately 6 cm. below the knee, there was an adherent clot, 5 to 6 cm. in length, similar in type to those described above.

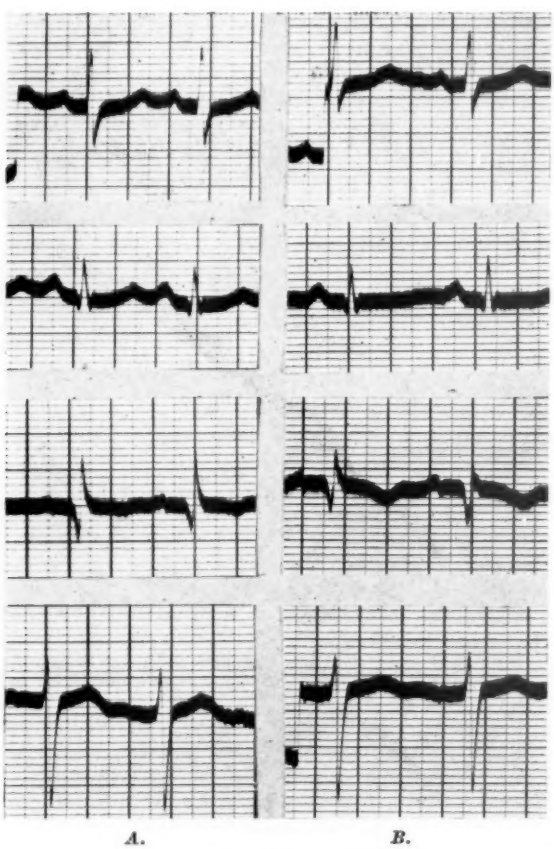


Fig. 4.—Case 4, F. W. H. *A.* October 23, 1940, several days after pulmonary embolism. *B.* October 29, 1940.

CASE 5.—D. J. M., aged 26 years, was considered healthy until he complained of weakness while at work on May 18, 1936. He remained in bed at home and had an unproductive cough without chills or fever. After the patient's death, his family physician supplemented this information with the history of chest pain radiating to the back and towards the left side, associated with a sense of dizziness and weak-

ness. When he tried to resume work, on May 25, he noticed weakness and debility, with slight shortness of breath on exertion which had not been present before.

An electrocardiogram (Fig. 5-*A*), taken May 25, showed sinus tachycardia and a rate of 125. Marked right axis deviation was present. A deep S wave occurred in Lead I, and the S-T segment was depressed in the same lead. The T wave was low in Lead II. The S-T segments were elevated in Lead II and Lead III. In Lead III there were a small Q wave and a deeply inverted T wave. Lead IV was normal. The patient was admitted to the hospital (May 26) because of the suspicious electrocardiographic abnormalities and his unusual history.

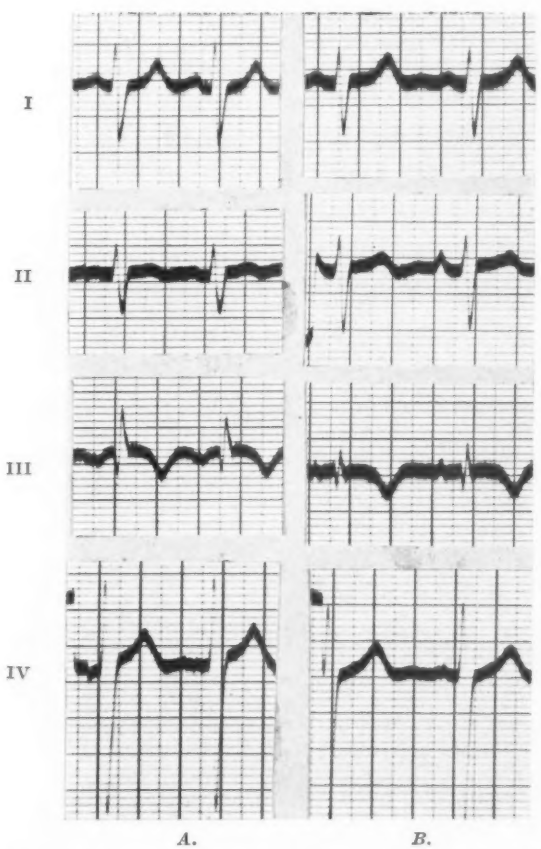


Fig. 5.—Case 5, D. J. M. *A*. May 25, 1936, several days after pulmonary embolism. *B*. May 26, 1936.

On physical examination the left border of his heart was 1 cm. outside the midclavicular line; the apex impulse was forceful and the rate was 120. The first mitral sound was split, but there were no murmurs. The blood pressure varied between 106/80, on admission, and 130/100, two days later. His leucocyte count was 11,800. A second electrocardiogram (Fig. 5-*B*), taken May 26, showed normal rhythm and a rate of 100, with right axis deviation still prominent. The T wave in Lead II was better defined. The QRS complex in Lead III was variable. He improved with rest in bed during the next three days. On the morning of May 30, after a good night's rest, he sat up in bed to wash, and became cyanotic and unable to breathe or call for aid, and died in a few minutes.

At autopsy his heart weighed 385 grams; the right ventricular wall measured 6 mm., and the left, 15 mm., in thickness. There was marked dilatation of the right ventricle. The valves and coronary arteries were normal. Gross and microscopic examination of the lungs failed to reveal any evidence of infarction or consolidation. In the right pulmonary artery there was a large adherent thrombus where the main vessel divides into the branches to the three lobes. It extended 6 cm. into the main artery of the right lower lobe. Many adherent granular thrombi were found in the other branches of the right pulmonary artery. The arterial branch to the left upper lobe contained an adherent, firm, ante-mortem thrombus; in the left lung the thrombi were more numerous in the smaller arteries than in the larger vessels. In the veins around the prostate and posterior part of the bladder there were numerous adherent thrombi. There was no thrombosis in the leg veins. Microscopically, the right ventricular wall showed much fatty infiltration between some of the muscle fibers near the pericardium.

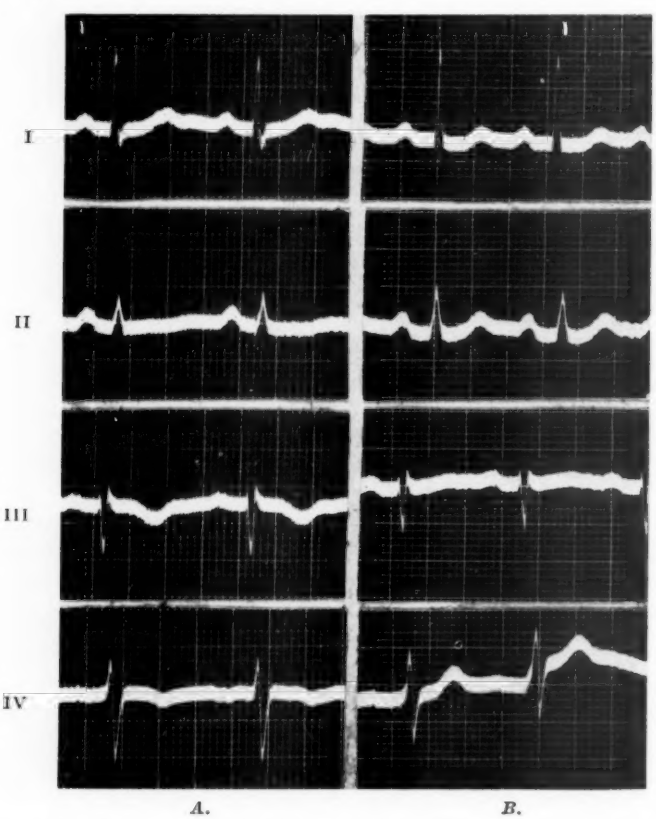


Fig. 6.—Case 6, F. C. *A*. November 14, 1940, 48 hours after second attack. *B*. March 2, 1941, follow-up record.

CASE 6.—F. C., an obese housewife, 61 years of age, tripped on a threshold on October 15, 1940, and suffered a fracture and dislocation of her left ankle. Reduction was successfully accomplished on the following day under gas and oxygen anesthesia. The patient improved until November 7, when she experienced an attack of pain beneath the upper part of the sternum, accompanied by quickened respiration. Rapid improvement followed without special treatment. While on a bedpan on November 12, she complained of severe substernal pain and temporarily lost con-

sciousness. A nurse in attendance observed that she was cyanosed and that her respirations were rapid and shallow. Her body became cold and clammy, her pulse was weak, the pulse rate was 130, and her blood pressure fell to 90/60. Later the patient said it was painful to breathe deeply; the pain was felt in the upper part of the left arm and in the left side of the chest. There was no hemoptysis. For an unstated time previous to this attack she had had pain in the calf of her left leg, but it was not of sufficient severity to cause her much concern.

A week later, on November 14, physical examination showed slight cyanosis of the lips. The neck veins were not distended. The left border of cardiac dullness was 8 cm. from the midsternal line, 0.5 cm. inside the midclavicular line. The rhythm was normal, and the rate was 70. A faint aortic systolic murmur was heard. The pulmonic second sound was slightly louder than the aortic second sound. The blood pressure was 106/70. A few moist râles were present along the left costal margin. Edema of the left leg was observed. There was definite tenderness to pressure on the left calf and along the inner aspect of the thigh up to the fossa ovalis. The girth of the limbs just below the tibial tubercles was 16.5 cm. on the left and 14.8 cm. on the right.

An electrocardiogram (Fig. 6-*A*) on November 14 showed normal rhythm and a rate of 75. In Lead I a small S wave was present, and there was slight depression of the S-T segment. In Lead II the T wave was slightly diphasic. In Lead III a Q wave was prominent and varied somewhat with the respiratory phase, and the T wave was negative. In Lead IV an R wave was present, and the T wave was inverted and shallow.

The patient improved considerably during the winter months. An electrocardiogram (Fig. 6-*B*) on March 2, 1941, showed normal rhythm and a rate of 85 to 90. The S wave in Lead I had disappeared, and the T wave in Lead II was upright and of normal amplitude. The QRS complex in Lead III was still largely inverted, and the deflections varied with respiration, as recorded in the first tracing. A high position of the diaphragm could best explain these variations in Lead III. In Leads II, III, and IV the T waves had become upright. This record was, therefore, normal.

CASE 7.—L. S., a single woman, aged 27 years, was admitted to the hospital April 30, 1938, with severe right upper quadrant pain radiating around to her back, which was aggravated by deep breathing. The pain began fourteen hours before entry, and was only slightly relieved by morphine. There were no chills, although she felt cold. She was nauseated, but did not vomit. There was no history of jaundice or stool changes. The record did not mention dyspnea, increased respiratory rate, or tachycardia. A month previously the patient had had tonsillitis and a sore throat for four or five days. Eleven days before admission she complained of migratory arthritis, involving the right ankle, right knee, and left wrist.

Physical examination showed a moderately ill woman who was breathing rapidly; her alae nasae were visibly active. There was evidence of localized consolidation at the base of the right lung. Gallop rhythm was present. The heart was not enlarged. The temperature was 104°, the pulse rate, 120, and respiratory rate, 25 to 30. The leucocyte count was 11,000. The diagnoses considered were (1) lobar pneumonia, (2) acute rheumatic fever, with pulmonic involvement, and (3) acute cholecystitis. Roentgenologic examination of the chest on April 30 showed a transverse heart, a high diaphragm on the right side, and haziness in the bases of both lungs. The sputum was negative for pneumococci, and on culture gave a few colonies of alpha and beta hemolytic streptococci. A second roentgenogram, taken May 2, showed definite consolidation of the right lower lobe; this was interpreted as pneumonia.

An electrocardiogram (Fig. 7-*A*) on May 2 showed normal rhythm, a rate of 105, and a small S wave in Lead I. There was a prominent Q wave in Lead III. The

T wave in Lead IV was inverted. The possibility of pulmonary infarction was suggested because of these changes, together with the history. She improved until May 6, when she suddenly developed a new pain in the right lower, anterior part of the chest and a slight cough without sputum. A roentgenogram on this day showed, in addition to the density in the right lower lobe, as before, other round areas of increased density in the middle and lower portions of the right lung. There were linear scars in the lower lobe of the left lung.

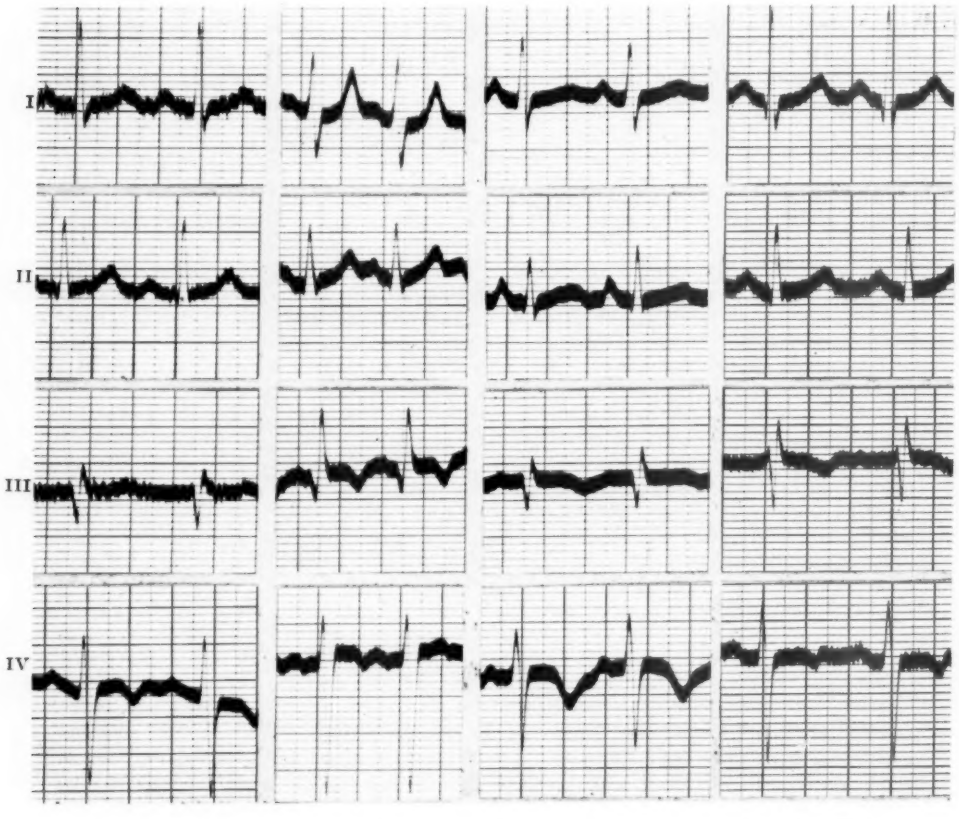


Fig. 7.—Case 7, L. S. *A*. May 2, 1938, 60 hours after first attack. *B*. May 18, 1938, 5 hours after attack of dyspnea, collapse, and side pain. *C*. May 23, 1938, clinically improving. *D*. April 2, 1941, no attacks since May, 1938.

The course of her illness from this date was very stormy. She had a series of seven attacks characterized by sudden onset of pain in either the right or left side of the chest, severe dyspnea and tachycardia, and, in addition, a fall in blood pressure. Hemoptysis occurred at intervals. The periods between the attacks were very variable, at times four days, at other times, ten days. The patient became extremely apprehensive, for she did not know at what hour she might be seized by another frightening attack of severe dyspnea, cyanosis, and collapse. Confirmatory evidence of the pulmonary involvement was obtained by numerous detailed studies on this patient. The electrocardiograms (Figs. 7-*B* and *C*) at first indicated strain on the right side of the heart and the state of acute cor pulmonale. Later, as the patient improved, the right axis deviation abated. During her hospital stay no physical signs of phlebitis were found.

Six months later she was well. Her heart was normal in size, and there were no murmurs. The blood pressure was 135/95. Almost three years after her discharge from the hospital, an electrocardiogram (Fig. 7-*D*), taken in the upright position, showed normal rhythm and a rate of 105. Right axis deviation was not present. Lead III was inverted, and there was slight inversion of the T wave in Lead IV. She looked well and had no complaints. She was moderately obese, and her heart was transversely placed.

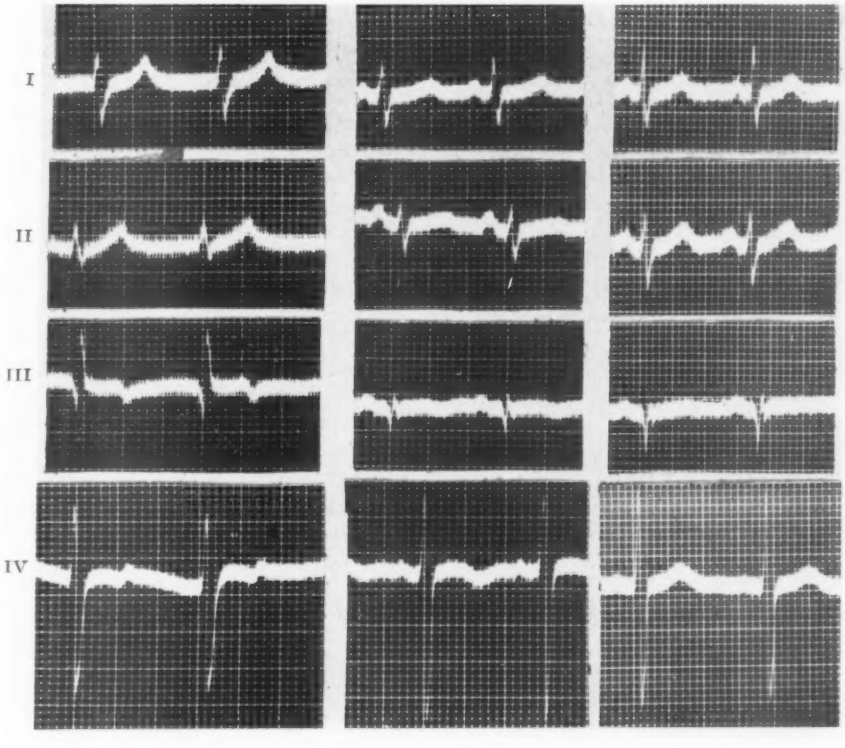


Fig. 8.—Case 8, C. C. *A*. October 3, 1938, 16 hours after first attack. *B*. October 7, 1938. *C*. March 3, 1941.

CASE 8.—C. C., a 52-year-old man, entered a hospital on September 21, 1938, where cholecystectomy and appendectomy were performed under spinal anesthesia on the following day. Convalescence was uneventful except for an unexplained, slight fever of 99° to 100°. On the tenth postoperative day, October 2, when he "dangled" for the first time, he was suddenly seized with an attack of breathlessness and substernal heaviness. He became pale, cold, and clammy, his heart rate was 140 and his pulse of poor quality, and his blood pressure was 70/60. Examination of his chest showed nothing abnormal. His heart was not enlarged, the sounds were poor, and the pulmonary second sound was not accentuated. His neck veins were not visibly distended. His leg veins appeared normal. On the sixteenth, twentieth, and twenty-sixth postoperative days he had similar but less severe attacks, during which he expectorated bloody sputum. He was discharged, symptom-free, on November 2, 1938.

An electrocardiogram on October 3 (Fig. 8-*A*), sixteen hours after the first attack, showed normal rhythm, a rate of 100, and right axis deviation. A deep S wave was present in Lead I. In Lead III a Q wave was present, and the T wave

was small but sharply inverted. The T wave in Lead IV was diphasic. A tracing (Fig. 8-*B*) four days later, on October 7, 1938, the fifteenth postoperative day, showed normal rhythm, a rate of 100, and a tendency towards low voltage. The degree of right axis deviation was less than in the first record. The depth of the Q wave and the inversion of the T wave in Lead III were much diminished. In Lead IV the T wave showed definite, but shallow, inversion. A subsequent tracing (Fig. 8-*C*), on March 3, 1941, showed normal rhythm and a rate of 95. An S wave persisted in Lead I. In Lead II the T wave was normal and in Lead IV the T wave had become upright.

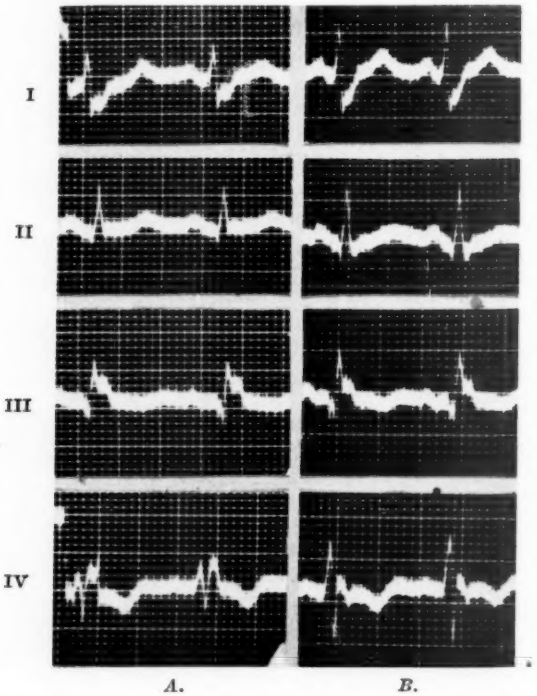


Fig. 9.—Case 9, M. C. *A*. March 5, 1940, 8 hours after second attack. *B*. April 28, 1940, approximately 7 weeks after last attack.

CASE 9.—M. C., a 60-year-old woman, entered the hospital February 23, 1940, a few hours after a fall. She was found to have a fracture of the neck of the left femur. On March 1, the hip was nailed under spinal anesthesia. Prior to this time there had been no symptoms suggestive of cardiac or pulmonary disease. Two days after the operation the patient complained of a sudden pain at the lower end of the sternum; this pain was of short duration. It was followed on the same day by the expectoration of bloodtinged sputum and occasional clots. Her temperature before and after the operation varied from 99° to 100° F. Physical examination on March 3 showed that the heart was normal. A few crackling râles were heard in the upper part of the chest and axilla on the left side. On the fourth postoperative day, March 5, she experienced a sharp pain at the right costal margin, made worse by deep breathing and relieved by a binder. The temperature and pulse and respiratory rates were increased. The patient was apprehensive, cold, and clammy. A pleural friction rub was heard in the painful area, and it was observed that the pulmonic second sound was accentuated.

An electrocardiogram (Fig. 9-*A*), taken eight hours after this second attack,

showed right bundle branch block, with a wide S wave in Lead I, and a rate of 105. There was a gradual ascent of the S-T segment in Lead II. There were a Q wave, splintering and slurring of the QRS complex, and an inverted T wave in Lead III. The R wave in Lead IV was upright, and the T wave was deeply inverted. A roentgenogram of her chest showed an area of increased density in the right lower portion. Again on the ninth and eleventh postoperative days, sharp pains occurred in the left side of the chest. Gradually she improved and did well for six weeks. Then once again she experienced pain in the right side of her chest; it lasted this time for twenty-four hours, and was followed by expectoration of blood. At this time she complained of soreness and swelling in the lower part of the left leg.

An electrocardiogram (Fig. 9-*B*), taken April 28, 1940, showed persistence of the right bundle branch block. The S-T segment in Lead II was isoelectric, and the T wave was upright. The T wave in Lead III was only slightly inverted. There is no evidence available to indicate whether the bundle branch block appeared as the result of the acute right ventricular dilatation or whether it existed prior to her accident. She improved considerably, and, one year later, could walk well without discomfort. She had no further chest pain.

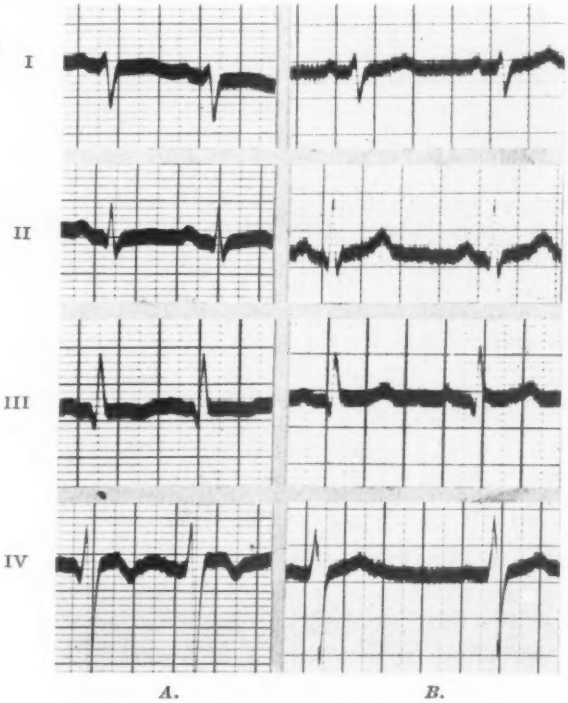


Fig. 10.—Case 10, I. W. *A*. May 10, 1939, 4 days after first attack. *B*. August 5, 1941.

CASE 10.—I. W., a single, 27-year-old man, had a typical attack of acute appendicitis on April 15, 1939, and was subjected to an appendectomy on the following day. His convalescence was satisfactory until May 6, when he experienced severe substernal pain, with collapse and dyspnea, while sitting in a chair. On physical examination he was ashen, sweating profusely, and had cold extremities, with peripheral cyanosis. His cervical veins appeared full, but not markedly distended. The heart rate was 125, and the blood pressure was 80/40. The leucocyte count was 13,500. Pulmonary embolism was suspected, and a constant intravenous

infusion of heparin in physiologic salt solution was started at once. The clotting time was kept at approximately forty minutes. No evidence of peripheral phlebitis in his legs was discovered. Neither cough, dyspnea, nor pain was present twenty-four hours after the attack. A roentgenogram of the chest on May 7 showed no evidence of disease. On May 10 another roentgenogram of the chest revealed a large area of hazy density, rounded in the lateral view, at the base of the right lung in the costophrenic angle, and a small dense area in the base of the left lung. These were interpreted as the result of infarction.

An electrocardiogram on May 10 (Fig. 10-*A*) showed normal rhythm, a rate of 120, and marked right axis deviation. The T waves were low in Lead I and Lead II, slightly inverted in Lead III, and inverted in Lead IV. A Q wave was present in Lead III.

The heparin was stopped arbitrarily on May 13. An electrocardiogram on this date showed normal rhythm and a rate of 115. The right axis deviation was less marked, and the T waves in Lead I and Lead II were upright. In Lead III a small Q wave and an inverted T wave were seen. In Lead IV the T wave was definitely inverted. On May 16 the consolidated area in the base of the left lung appeared roentgenographically as two fairly well-defined areas, both of which were believed to represent infarcts. Three days later (May 19) the patient complained of stiffness in his left calf and thigh. It was normal in appearance, and its girth was not increased. The leucocyte count was 9,600. The temperature and pulse rate were normal. On May 20, he complained of pain in the left calf. His temperature rose to 100° and his pulse rate to 90. There was edema of the entire leg; its girth was now uniformly greater than the right. Homan's sign, namely, the induction of pain in the calf region by dorsiflexion of the foot, became positive. A diagnosis of acute thrombophlebitis of the deep veins, with evidence of superficial phlebitis in the lesser or short saphenous vein, was made. Ligation of the femoral vein distal to the junction of the vena profunda femoris was performed. The long saphenous vein was ligated separately. Moderate swelling of the thigh was present for forty-eight hours, and then diminished. The pain in the calf disappeared six days after operation, and he was walking on the eleventh postoperative day.

Eleven months later he was quite well, and had had no recurrence of pulmonary embolism. A follow-up electrocardiogram on August 5, 1941 (Fig. 10-*B*), showed sinus arrhythmia, a rate of 70 to 80, and right axis deviation, which, although somewhat decreased, had persisted. A small Q wave was still present in Lead III. All of the T waves were upright.

REVIEW OF THESE TEN CASES

In this series there were three cases (1, 6, 9) in which pulmonary embolism followed bone injuries in women over the age of 60, with one fatality. There were three cases of postoperative embolism (3, 8, 10); two of these patients were in the third decade, and there was one fatality. Three patients (4, 5, 7) presented pulmonary symptoms from the beginning of their illness, and one (2) had varicose veins and phlebitis. In the miscellaneous group of four patients, there were three fatalities. Nine patients had two or more attacks of infarction. The tenth patient had only one. He was probably saved from further attacks by the ligation of his femoral vein. All five fatalities were caused by a major obstruction, which was the second attack in four cases, and the third in one.

The electrocardiogram gave the first suggestive laboratory evidence of the correct diagnosis in three cases (4, 5, 7); in the others, the electro-

cardiographic changes were confirmatory of the clinical diagnosis. Follow-up studies revealed an almost complete return to the normal pattern in Cases 1 and 6, and a partial return in Cases 4, 7, 8, and 10. Among the survivors, right axis deviation persisted in three cases (8, 9, 10).

Peripheral thrombosis or phlebitis in the lower extremity was present or suspected clinically in five cases (2, 4, 6, 9, 10). Thrombosis of the popliteal vein was found at post-mortem examination in two cases (1 and 4), and in the prostatic venous plexus in one (5). Venous thrombosis in the legs was not suspected or discovered in three patients (3, 7, 8), two of whom had acute attacks on the eighth and tenth days post-operatively, respectively. Four patients (2, 4, 5, 7) were ambulatory when they had their first attack. The remaining six had been in bed at least six days. The onset was not clearly acute in Cases 4 and 5. A wide S wave in Lead I occurred in Cases 3, 4, 5, 8, 10, and (?)9, and may be comparable to the transient right bundle branch block reported by Durant, et al.[9]

OTHER CASES OF PULMONARY EMBOLISM

To evaluate the electrocardiographic changes in pulmonary embolism, a series of ninety-two other patients with this condition who had been seen in the wards of the Massachusetts General Hospital and in private practice was studied. Approximately 50 per cent of these patients had electrocardiograms taken within twenty-four hours of the pulmonary embolism. No patient was included who did not have an electrocardiogram taken within ninety-six hours of the attack. We found that only about one case in six of pulmonary embolism had been studied electrocardiographically.

The diagnosis was confirmed by autopsy in forty-two cases. In the remaining fifty cases, the clinical diagnosis was adequately supported by physical and laboratory evidence. The cases were analyzed in two groups, namely, those in which the diagnosis was confirmed at autopsy, and those in which the diagnosis was only clinical. Each group has been subdivided into (a) cases in which the features of shock predominated at the onset of the attack, and (b) cases in which signs and symptoms of pulmonary infarction, without shock, characterized the clinical picture.

Forty-Two Autopsy Cases.—Thirty-nine were cardiac patients (hypertensive and/or coronary heart disease, twenty-four; rheumatic heart disease with mitral stenosis, ten; miscellaneous, five). Many of these showed multiple pulmonary infarcts at autopsy.

(a) In thirteen of the forty-two cases the clinical features of *shock* predominated at the onset of the attack. Of these cases, organic heart disease occurred in eleven, and, in almost all, coronary disease was the etiologic factor (there were no cases of rheumatic heart disease in this group). No change in the already abnormal electrocardiograms occurred after the attack in six of this group of eleven. Of the remaining

five cardiac patients, one showed all the characteristic features of the acute cor pulmonale pattern except right axis deviation; another exhibited a temporary shift from slight left towards right axis deviation, and two others showed depression of the S-T segment in Lead I and in Lead II (digitalis influence was excluded) as the principal electrocardiographic alterations. The remaining cardiac patient developed auricular fibrillation coincident with the attack.

The two patients without heart disease in this group were of considerable interest. Auricular flutter was precipitated in one, and a tendency towards right axis deviation (small S wave in Lead I) developed in the second. In common with four cardiac patients (three of whom showed no electrocardiographic change, whereas the fourth developed auricular fibrillation), these patients had only a few small pulmonary infarcts at autopsy. Certainly the mechanical factor of obstruction in the pulmonary arterial bed was minimal in these cases.

(b) In twenty-nine of the forty-two cases, *the signs and symptoms of pulmonary infarction,* without shock or collapse, predominated clinically. Complicating factors, which of themselves could modify the electrocardiogram, were present in all cases in this group. Organic heart disease was present in twenty-eight cases, and full therapeutic doses of digitalis were being administered when the electrocardiogram was made in the remaining one. Nevertheless, temporary changes that were believed to be significant evidence of some degree of acute cor pulmonale occurred in ten cases. In three additional cases, auricular fibrillation developed. In each case the abnormal rhythm was apparently precipitated by a small embolus. The electrocardiographic changes which occurred included, first, the temporary appearance of a small S wave in Lead I or the temporary disappearance of previously existing, slight, left axis deviation; and, second, a depression of the S-T take-off and segment in Lead II, and less frequently in Lead I. These alterations were correlated with significant thrombotic obstruction in the pulmonary arterial bed at autopsy. Large terminal emboli, if present, were excluded. Temporary deviation of the electrical axis towards the right was the most common electrocardiographic alteration.

Lead IV-F was available in thirty-one of the forty-two cases. Inversion of the T wave, with an upright R wave, occurred in eight cases, and, in three cases, a diphasic appearance of the T wave occurred. Five patients had an abnormal T wave prior to the pulmonary embolism. In the remaining fifteen cases the T wave was upright.

We believe that those patients who developed temporary deviation of the electrical axis towards the right or a depression of the S-T segment in Lead II or in Lead I actually had some degree of acute cor pulmonale at the time the electrocardiogram was made, even though the clinical manifestations of the condition were not then apparent.

Fifty Cases of Pulmonary Embolism, Without Autopsy.—Organic

heart disease was present in at least twenty-seven of these cases, i.e., coronary heart disease in twenty-one, and rheumatic heart disease in six. The electrocardiographic changes mentioned refer to those recognized after an attack of pulmonary embolism.

(a) There were sixteen cases (seven were cardiac patients with coronary artery disease and/or hypertensive heart disease) in which the signs and symptoms of *shock* predominated at the onset of the attack. No patient showed all of the features of the typical electrocardiographic pattern of acute cor pulmonale. Three patients with hypertensive heart disease developed the pattern except for right axis deviation. Two others showed electrocardiographic changes which were deemed significant evidence of some degree of acute cor pulmonale. These included a small S wave in Lead I and a low take-off of the S-T segment in Lead I, or in Lead II, and a Q wave and inversion of the T wave in Lead III. Variable, slight inversion of the T wave in Lead IV accompanied these alterations in the limb leads.

Lesser, temporary, electrocardiographic changes occurred in four cases. They appeared individually, and perhaps indicate that a slight degree of acute cor pulmonale was caused by the pulmonary embolus. These alterations were the appearance of a small S wave in Lead I, a low S-T take-off and segment in Lead II or in Lead I, and inversion of the T wave in Lead IV. Shallow inversion of the T wave in Lead IV occurred as an isolated abnormality in two additional cases. This is of questionable diagnostic significance, but is consistent with a mild, transient degree of acute cor pulmonale. Since Lead IV-F was employed, it can be said that the chest electrode may have been on the border of the right ventricle, or was so influenced by it, that an indeterminate T wave resulted.

(b) Thirty-four patients presented the *clinical signs and symptoms of pulmonary infarction,* without shock or collapse. Of these, twenty had heart disease. No typical electrocardiographic pattern of acute cor pulmonale was found. Small changes did occur in seven cases, including a small S wave in Lead I and a low take-off of the S-T segment in Lead I or Lead II. Auricular flutter developed in one patient coincident with the attack. There were no electrocardiographic alterations in the remaining twenty-six cases. This latter group included those patients whose previously abnormal records were unchanged by the attacks, and those whose electrocardiograms were still normal after pulmonary embolism occurred.

Summary of This Series of Ninety-Two Cases.—Co-existent heart disease was present in sixty-nine of these cases. In twenty-nine, symptoms of shock predominated at the onset, and, in sixty-three, the signs of pulmonary infarction without shock or collapse were predominant. Electrocardiographic changes which were considered suggestive of a minor degree of acute cor pulmonale were present in sixteen of the former

and in seventeen of the latter. The onset of auricular fibrillation was observed in four cases, and auricular flutter in two cases, in this series. Many cases of pulmonary embolism in the records were not studied electrocardiographically, and in others no electrocardiogram was taken until several days after the attack occurred. We believe, on this account, that the true frequency of helpful electrocardiographic changes after pulmonary embolism is probably greater than our figures indicate.

DISCUSSION

The terms "pulmonary embolism" and "acute cor pulmonale" are not synonymous. Not every patient with pulmonary embolism develops acute cor pulmonale, and hence the typical electrocardiographic changes do not always appear. If acute right ventricular strain were caused by an embolus, an electrocardiogram taken within a few hours of the onset of symptoms might be expected to show evidence of it. The degree of mechanical obstruction in the pulmonary circulation and, possibly, certain reflexes affecting the pulmonary vascular bed influence the length of time during which this evidence is manifested. The anoxia, and possibly also reflex coronary constriction, secondary to the pulmonary embolism, may perhaps act as additional factors to favor the development of the right ventricular dilatation of acute cor pulmonale, and may in themselves even influence the electrocardiogram.

During this study two interesting observations were made: (1) Electrocardiographic evidence suggestive of acute cor pulmonale was found after the occurrence of pulmonary embolism when the clinical signs of the condition were not apparent, and (2) symptoms of shock and collapse may predominate even with small emboli. Of the six cases in which this occurred, electrocardiographic signs of mild, acute cor pulmonale were present in only one. Before the degree of acute cor pulmonale which may exist temporarily in similar cases can be ascertained, further electrocardiographic observations must be made soon after the onset of symptoms.

Some factors which may modify the appearance, or even obscure the features, of the typical pattern are: (1) deviations from the normal caused by pre-existing heart disease; (2) the degree of mechanical obstruction to the pulmonary circulation; (3) the length of the interval between the attack and the taking of the electrocardiogram; (4) the presence of abnormal conditions which of themselves alter the electrocardiogram, e.g., toxic states, digitalization; and (5) the presence of abnormal rhythms.

Apparently, acute cor pulmonale may occur in varying degrees of severity. In the most marked cases there are the signs of dilatation of the right auricle and ventricle and the typical electrocardiographic pattern previously described; the lesser grades may or may not cause transient clinical signs, and may produce only temporary electrocardiographic changes of significance, namely, a tendency of the electrical axis

to deviate towards the right, evidenced most commonly by a small S wave in Lead I, or a low take-off of the S-T segment in Lead I or in Lead II, or a Q wave and inversion of the T wave in Lead III, or a negative T wave in Lead IV. In some instances the degree of right axis deviation may be slight; in others, the T wave in Lead IV may be upright. When the possibility of acute cor pulmonale arises, we recommend the use of multiple chest leads. The T wave is most likely to be inverted when the precordial electrode is over the right ventricle. Lead IV-F sometimes records the electrical potential from the right ventricle and sometimes from the left, more especially if left ventricular hypertrophy exists. This is probably very important in actual practice. Chest lead positions 2 and 3 should be explored when in doubt, that is, in the fourth intercostal space just to the left of the sternum, and midway between that point and the midclavicular line on the line from point 2 to the cardiac apex. Normally the T wave is upright in these two precordial leads, but in the case of the acute cor pulmonale it is inverted (more definitely than in the routine Lead IV).

Many tracings record only the tachycardia associated with the embolism. They are included in our study as those without significant electrocardiographic alterations, and classified as without change. The presence of organic heart disease, with an abnormal electrocardiogram, as in mitral stenosis or coronary heart disease with myocardial anoxemia —pulmonary infarction is a frequent complication in these cases—often limits the diagnostic value of the electrocardiogram in a suspected state of acute cor pulmonale.

The onset of abnormal rhythms and various types of heart block has been reported as a result of pulmonary embolism. Four cases of auricular fibrillation and two of auricular flutter were observed in our series. Five examples of increased duration of the S wave in Lead I have been mentioned above.

In evaluating the electrocardiogram of a patient who is suspected of having acute cor pulmonale as a result of pulmonary embolism, it is important to know how much time elapsed between the onset of the attack and the taking of the electrocardiogram. If the obstruction to the pulmonary circulation is small or is overcome soon after its occurrence, the embarrassment of the right ventricle will pass off rather rapidly. An electrocardiogram taken within a few hours of the attack may therefore afford the only means of recognizing it, for such signs as an S wave in Lead I, or an inverted T wave in Lead IV, often persist after the physical signs, if there were any, have disappeared. However, even these signs may have disappeared completely within twenty-four hours of the attack. This evidence can be available before roentgenologic signs of pulmonary infarction develop.

Many authors confirm the fact that coronary occlusion has been commonly confused with severe, acute cor pulmonale. This has been amply borne out in our experience. Several observers have mentioned the

clinical differential diagnosis and have indicated the important diagnostic value of the electrocardiogram. However, the electrocardiographic features may be confused in both of these conditions when the changes are atypical or equivocal. An accurate history and a careful appraisal of the physical signs remain of major importance in establishing the correct diagnosis. Serial electrocardiographic studies are then helpful in evaluating the status of the heart.

It is, incidentally, of great importance to recognize the fact that either condition may complicate or more or less set off the other (pulmonary embolism from stasis during convalescence from myocardial infarction, or myocardial infarction in a person with considerable coronary disease whose coronary circulation is decreased by pulmonary embolism); there

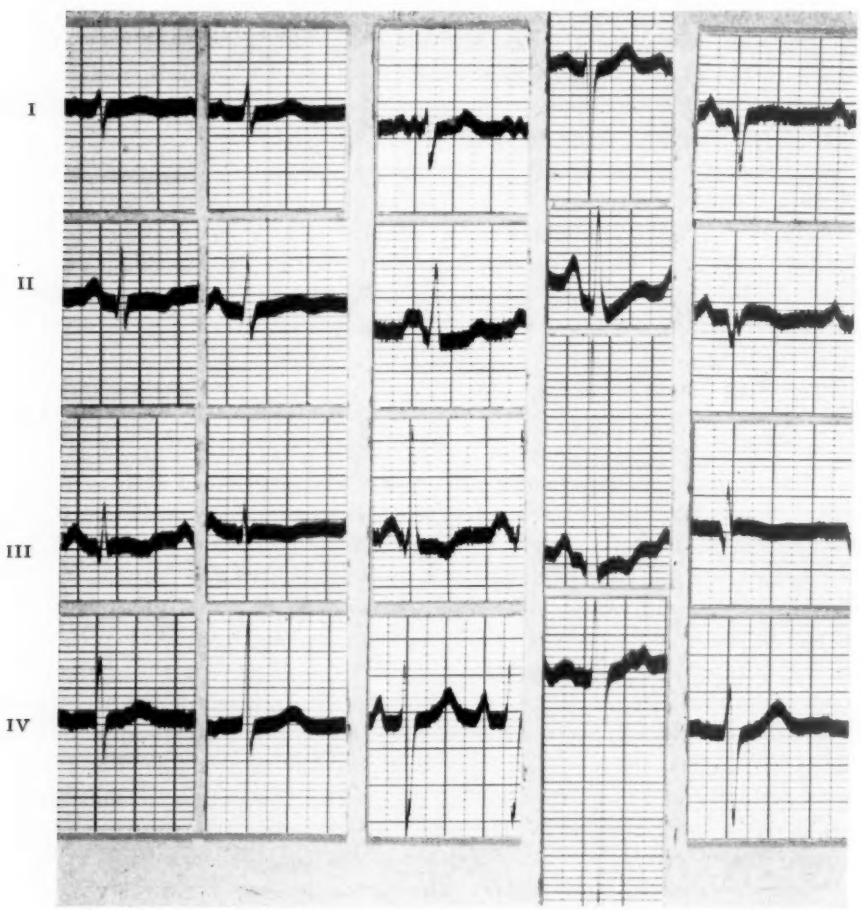


Fig. 11.—*A*, A. St. L. 1. Electrocardiogram of a normal heart in a patient of asthenic build. September 10, 1941. Sitting position. 2. September 11, 1941. Recumbent position. *B*, N. I. Electrocardiogram of a patient with mitral stenosis. August 25, 1941. *C*, O. M. Electrocardiogram of a patient with Tetralogy of Fallot. November 12, 1936. *D*, J. A. W. Electrocardiogram of a patient with recent posterior myocardial infarction. April 28, 1942.

then may be a double effect of the two conditions on the electrocardiogram. The complication, nay, even the precipitation, of one condition by the other has not been taken adequately into account in the past. Sometimes the anoxemia resulting from pulmonary embolism may produce transient changes in the electrocardiogram which may simulate somewhat, but not exactly, acute cor pulmonale, without the more persistent changes found with actual myocardial infarction. It is, of course, the posterior and not the anterior myocardial infarct or anoxic state that superficially resembles acute cor pulmonale in its effect on the electrocardiogram.

In three (4, 5, 7) of our ten cases, acute cor pulmonale was not considered until it was suggested by the electrocardiogram. Other examples very likely pass unrecognized, as almost happened in these cases. The large mortality among these patients and the discovery of thrombosed veins in their extremities suggest that timely diagnosis and operation on the affected veins should be the physician's goal. Prophylactic leg exercises, combined with more attention to the leg veins by the physician, and widespread recognition of the varied manifestations of pulmonary embolism should lead to a sharp decrease in the incidence of fatal pulmonary emboli, more especially among patients confined to bed. Bland thrombosis of the veins, the so-called phlebothrombosis, may baffle the most competent physician, and deliver a lethal embolus to the pulmonary circuit before it is recognized. In this connection the introduction of venography has been of considerable importance. With this technique the patent venous channels are outlined by a radiopaque dye, such as diodrast. Venous obstruction, especially in the deep veins of the leg, may thus be revealed. The appropriate veins can then be ligated and the danger from pulmonary embolism considerably reduced. Experience with venography suggests that discrimination in the selection of patients and improved technique will lessen the incidence of complications, such as local phlebitis at the site of injection.

A few additional electrocardiograms (Fig. 11, *A, B, C, D*) are herein presented, with brief clinical notes, because of their superficial similarity in some respects to the acute cor pulmonale pattern. They show normal rhythm and a rate of 100 or faster, with slight to moderate right axis deviation. A Q wave was present and an inverted T wave was often seen in Lead III. The T wave in the chest lead was upright. This group included asthenic persons with rapid heart rates, and persons with mitral stenosis, certain forms of congenital heart disease, and posterior myocardial infarction. They emphasize the fact that it is important to possess clinical knowledge of the patient in order to evaluate the record accurately.

SUMMARY

Ten patients with acute cor pulmonale, without underlying heart disease, five of whom died (three had post-mortem examinations), are

presented with their electrocardiograms to corroborate the observation that there is a typical electrocardiographic pattern in acute cor pulmonale; it is characterized by right axis deviation with a prominent S wave in Lead I, a depressed S-T segment in Lead II and often in Lead I, a Q wave and an inverted T wave in Lead III, and a diphasic or an inverted T wave in Lead IV-F. An upward convexity of the S-T segment in Lead III is common; an elevation of the S-T take-off in this lead occurs in a few cases. The cases were selected so that other factors which of themselves could have modified the electrocardiogram were excluded.

The electrocardiographic changes in an additional series of ninety-two cases of pulmonary embolism were reviewed. Co-existent heart disease occurred in sixty-nine. In twenty-nine cases symptoms of shock predominated; in sixty-three the signs of pulmonary infarction without shock or collapse predominated. Electrocardiographic changes that were considered indicative of acute cor pulmonale were present in sixteen of the former group, and in seventeen of the latter. In other words, the electrocardiogram gave indication of some degree of acute cor pulmonale in a little more than one-half of the cases when shock predominated, in a little less than one-quarter of the group without shock, and in about one-third of the entire series, including those patients who had abnormal electrocardiograms as a result of heart disease.

It is emphasized that "pulmonary embolism" and "acute cor pulmonale" are not synonymous terms. It appears that varying degrees of acute cor pulmonale occur, and that the electrocardiogram provides a means of evaluating the status of the heart, especially when clinical signs indicative of right-sided heart strain are not obvious.

It is our belief that anoxemia produced by a pulmonary embolus may cause infarction in cardiac muscle which is already the seat of severe coronary artery disease. When this occurs, the electrocardiographic changes are confusing and atypical.

Death is often caused by a second or third embolus. Prophylactic leg exercises, venography, and, if indicated, ligation of the femoral vein should reduce the incidence of fatal pulmonary emboli.

REFERENCES

1. Barnes, A. F.: Diagnostic Electrocardiographic Changes Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**: 11, 1936. Electrocardiographic Patterns, Baltimore, 1940, Charles C Thomas, p. 94.
2. Love, W. S., Jr., Brugler, G. W., and Winslow, N.: Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, Ann. Int. Med. **11**: 2109, 1938.
3. Stewart, H. J., Kirk, R. C., and Smith, J. J.: Electrocardiographic Changes in Pulmonary Infarction, Internat. Clin. **3**: 135, 1940.
4. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism, J. A. M. A. **104**: 1473, 1935.
5. Scherf, D., and Schönbrunner, E.: Ueber Herzbefunde bei Lungenembolien, Ztschr. f. klin. Med. **128**: 455, 1935.
6. Sokolow, M., Katz, L. N., and Muscovitz, A. N.: Electrocardiogram in Pulmonary Embolism, AM. HEART J. **10**: 166, 1940.

7. Horn, H., Dack, S., and Friedberg, C. K.: Cardiac Sequelae of Embolism of the Pulmonary Artery, Arch. Int. Med. 64: 296, 1939.
8. Wood, Paul: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography, Brit. Heart J. 3: 21, 1941.
9. Durant, T. M., Ginsburg, I. W., and Roesler, H.: Transient Bundle Branch Block and Other Electrocardiographic Abnormalities in Pulmonary Embolism, AM. HEART J. 17: 423, 1939.

ADDENDUM

Since the preparation of this paper an important article has been published by James Currens (The Electrocardiogram in Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **17**: 502, 1942). In an endeavor to shed more light on the problem, careful microscopic examination was made of the hearts in thirty cases of pulmonary embolism, with section of the coronary arteries every 5 mm. throughout their course, and, in addition, at least six sections from right and left ventricles of each heart. In five cases, recent infarction of the right or left ventricle was found, in one of which there was recent thrombosis of the right coronary artery, but in the remaining four no demonstrable occlusion of the coronary arteries. Currens writes as follows: "In appraising the electrocardiographic changes during suspected pulmonary embolism it should be borne in mind that no one electrocardiographic abnormality is consistently present in pulmonary embolism"; and in summary, he states: "The cause for the electrocardiographic changes in pulmonary embolism is considered, and strain on the right ventricle seems to be the dominant factor. The presence of a pulmonocoronary reflex following pulmonary embolism is difficult to prove, and it seems likely that any compromise in the coronary circulation is best explained by shock and an increase in pressure in the right side of the heart. The decrease in blood flow to the right ventricle from a decrease of arterial pressure gradient, plus an increase in work of the right ventricle may account for the occasional association of angina pectoris with pulmonary embolism. Evidence is presented to suggest that asphyxia does not appreciably affect the electrocardiogram in pulmonary embolism. The electrocardiographic pattern in pulmonary embolism is variable and the value of the precordial leads is stressed."

ON THE AMOUNT OF, AND CHANGES IN, THE RESIDUAL BLOOD OF THE HEART

GUSTAV NYLIN, M.D.
STOCKHOLM, SWEDEN

TODAY our knowledge of the capacity of the different heart chambers during life is extremely imperfect. On the other hand, as regards the volume of the whole heart, there are, in the earlier literature, accounts of a number of investigations carried out on autopsy material, such as those of Beneke,[1] Müller,[2] and Henle,[3] but these comprise data on only the weight of the muscular substance of the heart (Müller), or the volume of the muscular substance (Beneke). Beneke found that the adult male heart has a volume of about 300 c.c., which is in good agreement with Müller's statement that the weight amounts to about 300 Gm.

During recent years, Kahlstorf,[4, 5] Nylin,[6] Lysholm, Nylin, and Quarnå,[7] and Liljestrand, Lysholm, Nylin, and Zachrisson[8] have made contributions toward elucidation of the volume conditions of the heart in vivo. The last-mentioned authors found that the normal volume of the heart in seventy healthy adults (students) amounted, on an average, to 700 c.c. Judging from Beneke's work, which indicates that the muscular substance has a volume of about 300 c.c., this would imply that the capacity of the heart cavities would amount to about 400 c.c. (700 – 300) altogether. We do not at present know with certainty whether this is the case. For reasons which are easily understood, the volume of the heart cavities is difficult to define, and the measurements which have been made in vitro are only of limited interest. As far as can be ascertained, only Hiffelsheim and Robin,[9] and, considerably later, Hochrein,[10] arrived at any conception as to the volume of the heart cavities. Hiffelsheim and Robin made post-mortem wax casts of the four cavities and calculated their size by ascertaining the displacement of the wax casts. From five normal persons in Hiffelsheim and Robin's series I have calculated that the total volume of the four cavities of the heart averaged 617 c.c. On the other hand, Hochrein gives a mean value of 561 c.c., calculated from thirty cases. Hochrein's technique differed from Hiffelsheim's, in that he ascertained "the capacity," i.e., the volume of the heart cavities, by filling the cavities under a water pressure of 8 cm. and measuring the amount of water required. If 300 c.c. for the tissue of the heart is added to Hiffelsheim and Robin's and Hochrein's mean values of the total capacity of the heart, the estimated volume of the heart for the respective authors amounts to 917 c.c. and 861 c.c.

To what degree the heart is emptied during systole has been discussed by several authors. Rollett[11] says: "Im Leben entleeren sich beide

Received for publication June 20, 1942.

Ventrikel gleichzeitig und gleich oft in der Zeiteinheit und zwar bis zum Verschwinden ihrer Höhlung." On the other hand, Chauveau and Faivre,[12] Roy and Adami,[13] and Starling[14] have assumed that the heart does not expell the blood completely during systole. It may probably be assumed that, during life under physiologic conditions, and more especially under pathologic conditions, the heart is not completely emptied of blood during systole, but that larger or smaller, nay, even considerable, quantities remain in the heart cavities; in other words, there is a certain amount of residual blood.

At the present time the stroke volume of the heart can be fairly exactly ascertained by the gas methods, at least in healthy persons. Nylin[15] found that it amounted to a mean value of 71 c.c. in healthy adults in the recumbent position; the heart volume of these subjects, as ascertained roentgenologically, averaged 843 c.c. Unfortunately, in this work it was not stated in which phase of the heart beat the estimations were made, but it is probable that, in view of the long exposure times, they were made during diastole. If the volume of the tissue of the heart in these experiments is estimated as 300 c.c., this would imply a diastolic capacity volume for the whole heart of about 540 c.c. If this value is decreased by twice the stroke volume (142 c.c.), the amount of residual blood in the recumbent position would normally amount to about 400 c.c. and, in the standing position, to only about 200 c.c.

Under certain pathologic conditions, and especially in cases of advanced cardiac insufficiency, it is generally known that there is considerable enlargement of the heart which cannot be due entirely to hypertrophy of the musculature, but rather to dilatation of the heart. From this it follows—since the stroke volume does not increase, but decreases—that the quantity of residual blood increases, and, in many cases, must become extremely large. Of the volume of these quantities of residual blood in cardiac insufficiency we know practically nothing.

RADIOLOGIC ESTIMATIONS OF CHANGES IN HEART VOLUME (CHANGES IN RESIDUAL BLOOD)

With the introduction of the roentgenologic method of estimating the heart volume by Kahlstorf, Lysholm, Nylin, and Quarnå, Liljestrand, Lysholm, Nylin, and Zachrisson, and Jonsell,[16] possibilities of obtaining a more objective measure of the size of the heart were created. Moritz,[17] Binhold,[18] Kahlstorf,[19] Natvig,[20] Böhme,[21] Nylin,[22, 23] Liljestrand, Lysholm, and Nylin,[24] and Nylin, Sällström, and Ågren[25] have shown that the heart is subject to considerable volume changes, both physiologic and pathologic. The heart is considerably larger in the recumbent position than in the upright position. It is also subject to changes in size as a result of changes in intrathoracic pressure; this is shown in extreme form by the fact that, with Müller's test, the heart is consider-

ably larger than with extreme expiration and pressure, as in Valsalva's test. It has also been found that the heart is subject to a decrease in volume after pneumothorax has been induced. Muscular work also influences the size of the heart, in that the heart volume decreases after heavy muscular work. The above, mainly physiologic, changes in heart volume imply that the amount of residual blood undergoes considerable changes. These physiologic alterations in the amount of residual blood are summarized in Table I. Several of these particulars derive from a number of observations, and are the mean values; others comprise only single observations. As we see from the table, the changes in the quantity of the residual blood which occur with the transition from the standing to the recumbent position, and in the extreme conditions of Valsalva's and Müller's experiments, are very considerable, whereas those which take place during muscular work are of a much smaller order of magnitude.

TABLE I

PHYSIOLOGIC CHANGES IN THE AMOUNT OF RESIDUAL BLOOD OF THE HEART

1. Postural changes—mean increase in the heart volume in 11 healthy persons on changing from standing to lying position	269 c.c.
2. The effect of intrathoracic pressure—decrease in the heart volume with transition from MÜLLER's to VALSALVA's experiment	400 c.c.
3. The effect of muscular work—mean decrease in the heart volume in 12 healthy persons after heavy muscular work, in comparison with the volume before the work	35 c.c.

Under pathologic conditions the heart is subject to considerable changes in volume, which depend on the degree of decompensation. Comprehensive observations on this point have been collected in the course of years at the Seraphim Hospital. In 1939, Nylin, Sällström, and Ågren[25] reported that, of about one thousand estimations of heart volume made since 1933, at least one hundred showed more or less pronounced changes. From these investigations it emerges that the largest number of volume changes are met with in connection with variations in the degree of cardiac insufficiency. If repeated heart volume estimations are made in a cardiologic department, it will be found that such changes are common. As an example of extreme, reversible changes in the amount of residual blood intimately associated with the degree of decompensation, I shall cite one of my cases of mitral and tricuspid insufficiency. As the patient improved and the heart failure decreased, the amount of residual blood decreased by 400 c.c.; there was an increase of no less than 650 c.c. six weeks later, when severe decompensation had set in again. The patient did not recover from this attack of failure. At autopsy it was proved that an exudate in the pericardium, amounting to only 50 c.c., had not had any noteworthy influence on the heart volume. In cases of pronounced hypertension, when the blood pressure had decreased considerably after treatment, particularly con-

finement to bed, considerable decreases in the residual blood have been observed. In coronary disease, such as angina pectoris and coronary thrombosis, changes in the amount of residual blood of as much as 300 c.c. have been observed. In beriberi it has been proved that there is an increase in residual blood of 290 c.c. (Nylin[26]). In a case of severe secondary anemia the decrease in the volume of the heart amounted to 350 c.c. when the blood was restored to normal. In a case of obesity, a decrease in weight of 40 kg. led to a decrease of no less than 360 c.c. in the heart volume. As is well known, myxedema is accompanied by dilatation of the heart, which recedes rapidly with thyroid therapy. I personally have no estimations of the decrease in residual blood in such cases, but Warburg[27] and others have published such observations.

TABLE II

PATHOLOGIC CHANGES IN THE AMOUNT OF RESIDUAL BLOOD OF THE HEART

1. Reversible changes which depend on the degree of decompensation	100—800 c.c.
2. Hypertension—single observations	180 c.c.
3. Coronary insufficiency, angina pectoris	330 c.c.
4. Coronary thrombosis—single observations	350 c.c.
5. Beriberi—single observations	290 c.c.
6. Anemia—single observations	350 c.c.
7. Obesity—single observations	360 c.c.
8. A. (a) Decrease in the heart volume in a case of unilateral pneumothorax	200 c.c.
(b) Decrease in the heart volume in a case of unilateral pneumothorax	125 c.c.
B. Decrease in the heart volume in a case of bilateral pneumothorax	350 c.c.

Table II shows these pathologic changes in the amount of residual blood. They are of great importance for an understanding of the pathophysiology of cardiac insufficiency. It is probable that the increase in the amount of residual blood, even in the incipient stages of cardiac insufficiency, constitutes a compensatory mechanism by increasing the length of the fibres and consequently the effectiveness of the heart muscle, in accordance with Starling's law. By means of observations on the changes in heart volume under both physiologic and pathologic conditions, possibilities have been created of measuring quantitatively, to a certain extent, the changes in the amount of residual blood.

POST-MORTEM HEART VOLUME ESTIMATIONS AND CALCULATION OF THE AMOUNT OF RESIDUAL BLOOD IN VIVO

It has already been pointed out that Hochrein and others before him made occasional post-mortem estimations of the volume of the heart cavities. Hochrein points out especially that the quantity of blood in the different cavities of the heart generally exceeds very considerably the stroke volume, so that, even under physiologic conditions during systole, the heart would not evacuate all its contents. As far as I can discover, there is practically no information about such estimations on

clinical material. On twelve mainly normal hearts, Kahlstorf made a comparison between heart volumes, as ascertained roentgenologically and by the displacement method, on the heart post mortem, and found extremely good agreement. In co-operation with Ture Petrén, I made a series of estimations of the roentgenologic volume ante mortem and the post-mortem displacement volume, and obtained varying results. Sometimes the agreement was extremely poor, probably because of the fact that after death the heart undergoes a decrease in volume with rigor mortis. (These investigations have not yet been published.) In order to study more closely the amounts of residual blood during life, occasional investigations have been made in recent years at the Seraphim Hospital and the Sabbatsberg Hospital by means of roentgenologic volume estimations immediately before death. At a certain time after death another heart volume estimation was made, and, in immediate association therewith, at autopsy, all the vessels of the heart were ligated and the heart removed, after which its volume was ascertained by the displacement method. Then the heart cavities were opened and emptied of their blood, and the blood content of each cavity was measured. By this means it was possible (1) to control the roentgenologic volume estimations by the displacement method, and (2) to detect a post-mortem decrease in volume, and thus calculate approximately the total capacity of the cavities during life. More exact data on these investigations in two carefully studied cases are given below.

The first case was that of a 69-year-old man who for ten years had suffered from progressive cardiac insufficiency, associated with coronary sclerosis. He was treated on eight different occasions at the Seraphim Hospital. During the last few years the heart volume was constant, on the whole, at about 2,000 c.c., so that this was a case of cor bovinum. At the last visit to the hospital his insufficiency was refractory to all therapy, and the roentgenologic heart volume amounted to 2,500 c.c. Four and one-half hours after death another roentgenologic estimation of the heart volume was made, and showed the amazing decrease of 1,220 c.c. Twenty-four hours after death the heart volume was measured by the displacement method and found to be 1,250 c.c., which agrees well with the roentgenologic heart volume post mortem. The blood content of the cavities of the heart post mortem was measured and found to be 500 c.c. Thus, in all, the calculated quantity of residual blood during life—apart from the slight double stroke volume of about 100 c.c.—amounted in this case to no less than 1,750 c.c. (2,500 – 1,250 + 500).

The second case was that of a 44-year-old woman who, from the age of 7 years, had suffered from valvular disease, the cause of which was unknown. She was admitted to the Sabbataberg Hospital Aug. 14, 1940, with severe cardiac insufficiency and grave signs of stasis. She had all the symptoms of mitral stenosis and tricuspid insufficiency, with a positive venous pulse. The venous pressure was 34 cm. She had an enlarged liver and general anasarca, and also pronounced cyanosis. She was refractory to all therapy. She was kept alive only by administering pure oxygen through a Boothby respiration mask. She died August 28, two weeks after admission. The roentgenologic estimation ante mortem showed a heart volume of 2,400 c.c., i.e., 1,850 c.c. per m^2 of body surface; this was therefore an enormous heart in proportion to the small thorax. The configuration of the heart was remarkable. It might almost have been thought that pericarditis was

present, but this did not appear to be the case. A roentgenologic heart volume estimation was made post mortem, but unfortunately the sagittal projection was not successful. In the frontal projection, at least, the heart had decreased, although not very much, in both length and breadth post mortem. As in the preceding case, all the vessels were ligated at autopsy, and the volume of the heart, as estimated by the displacement method, was found to be 1,335 c.c. At autopsy, 150 c.c. of blood ran from the heart cavities. The pericardium contained 440 c.c. of fluid. Thus, the post-mortem volume of the heart, together with the blood which ran out and the pericardial fluid, amounted to 1,925 c.c., which is not inconsiderably less than the volume as ascertained ante mortem. It is possible that this discrepancy was real, and caused by changes in the quantity of the residual blood with the onset of rigor mortis. In addition, at autopsy the quantity of blood in the right auricle was measured and found to be 625 c.c.; the left auricle contained 290 c.c. The ventricles contained practically no blood. The volume of the heart tissue was 390 c.c. Thus the two auricles contained 915 c.c. at autopsy, and 150 c.c. had run out. Therefore, the amount of residual blood post mortem was 1,065 c.c. If it is correct in this case that, with the onset of rigor mortis, the heart decreased by 475 c.c. (2,400 – 1,925) this would imply that during life the amount of residual blood was 1,065 c.c. plus 475 c.c., or 1,540 c.c. Both the right and left auricles contained very considerable quantities of residual blood, and this was, for the most part, the cause of the configuration of the heart in the roentgenogram ante mortem. The cause of the enormous dilatation of the auricles proved, at autopsy, to be extreme mitral and tricuspid stenosis.

From these two examples it appears that the quantity of residual blood during life in certain cases of grave heart insufficiency may approach several liters. By means of roentgenologic ante- and post-mortem volume estimations, combined with estimations by means of the displacement method and measurement of the blood content of the different chambers of the heart post mortem, it has become possible to study more closely the amount of residual blood in different cases during life.

THE IMPORTANCE OF MEASURING THE CIRCULATION TIME IN ESTIMATING THE AMOUNT OF RESIDUAL BLOOD

The fundamental symptom of cardiac insufficiency when the patient is resting in bed is congestion of either the lungs or the vena cava area, or both. In estimating the degree of congestion in the vena cava area, the usual method is to measure the pressure in a vein of the arm; and, without going into further detail, I will only say that venous pressure normally amounts, at most, to 10 cm. of blood. Unfortunately, we have no method of measuring the pressure in the pulmonary veins. The only possibility at present of estimating objectively the presence and degree of lung congestion is by means of roentgenologic examination.

Blumgart and Weiss's[28] method of measuring the circulation time opened new possibilities for judging the degree of congestion. These investigators injected radium emanation into the vein of an arm. Then, by a special method, the time of arrival of the radium emanation in the right half of the heart was established, then in the left half, and finally in the arterial system, e.g., in an arm. The method was simplified later, and other test substances, such as decholin, saccharin, fluorescein, hista-

mine, lobeline, and magnesium sulfate were used. I employ a 20 per cent solution of decholin, which is injected into the vein of an arm, and the time which elapses after the injection until the patient becomes aware of a bitter taste is measured. In this way the circulation time from the vein of the arm by way of the right half of the heart, the lungs, and the left half of the heart out into the arterial system to the tongue, is measured. Several authors have used this method and have reported results that are in general agreement. Thus, according to Tarr, Oppenheimer, and Sager,[22] the normal circulation time varies between 10 and 16 seconds. When congestion is present, either in the lungs, the vena cava area, or both, the circulation time is considerably prolonged, as has been clearly established by many authors during recent years. Congestion increases the circulation time to as much as 60 seconds or more.

Since 1933 we have measured the circulation time at the Seraphim Hospital and the Sabbatsberg Hospital in a considerable number of cases of heart disease. With regard to measurements of the circulation time alone, we have had, on the whole, the same experiences as other authors, but we have compared these measurements with the results of other examinations, particularly heart volume and venous pressure. It has been proved, as I shall show, that factors other than congestion, i.e., increased venous pressure, affect the circulation time.

During recent years we have directed our attention not only to the time that elapses from the time of injection until the bitter taste is perceived, but also to the patient's taste sensation. Thus, in several cases we have been able to fix the time of both maximal taste sensations and cessation of sensation, which normally occurs, at the latest, about 30 seconds after the injection.

We have followed several patients with cardiac insufficiency with repeated measurements during their return to compensation, as in the following case:

The patient was 55 years of age, and had hypertension and conjestive heart failure. At the first examination the patient had anasarca, a heart volume of 2,100 c.c., and a venous pressure of 24 cm. Measurement of the circulation time: the first perception of taste was much delayed, i.e., 40 seconds, and the bitter taste did not disappear until after 70 seconds. Somewhat over three weeks later the congestion had diminished; the body weight had decreased by 5 kg.; the venous pressure had decreased to about half, i.e., 13 cm.; the time interval for the first taste sensation was considerably shortened, i.e., 18 seconds; and the duration was certainly shorter, i.e., 55 seconds, but nevertheless was considerably longer than normal. A month later, when the congestion and edema had disappeared, and the patient had lost 17 kg. in weight, and the venous pressure was only 6 cm. Circulation time: the first taste perception occurred after 20 seconds, was maximum at 30 seconds, and ceased at 40 seconds. The heart volume had decreased to 1,800 c.c., but the heart was still considerably enlarged.

The duration of the taste sensation was still prolonged, a fact to which, in my opinion, the greatest attention should be given. The signifi-

cance of the fact that, with an enlarged heart and no congestion, the circulation time is prolonged as regards both the first taste sensation and, above all, its duration, probably is that the enlarged heart is dilated and contains a considerable amount of residual blood. When the heart contains a large amount of residual blood, it must take a considerably longer time for the heart to empty its blood, including the decholin, than for a heart of normal size with a small amount of residual blood. As examples of prolonged circulation time—measured with decholin—and, above all, prolonged duration of the taste sensation when the heart is dilated and there are no signs of congestion, the following three cases are presented.

CASE 1.—G. R., a fitter, aged 62 years, had coronary sclerosis and hypertension, and had been short of breath on exertion for several years. His general condition was good. The sedimentation rate was 3 mm. in one hour. The urine was normal. The patient had no fever.

Physical examination showed no symptoms of cardiac insufficiency at rest. The blood pressure was 170/110. There were no cardiac murmurs. The patient had auricular fibrillation and a venous pressure of 8 cm. Circulation time: The first taste sensation occurred at 35 seconds, and taste perception ceased at 55 seconds.

Roentgenologic examination showed that the heart measured 17.5 in length, 13 in breadth, and had a sagittal diameter of 15 cm. The volume was 1,430 c.c., i.e., 700 c.c. per m^2 of body surface. The heart was generally enlarged, with some preponderance of the left ventricle. There was no congestion in the lungs. The cardiac pulsations were rather small and irregular.

The electrocardiogram showed auricular fibrillation, with a ventricular rate of 60 per minute. QRS measured 0.09 seconds. T_1 was positive, T_2, positive, and T_3, isoelectric. The S-T interval was slightly depressed in Leads I and II. The ventricular complexes were slightly notched in all leads. Diagnosis: Auricular fibrillation and partial bundle branch block.

CASE 2.—The patient was a 19-year-old schoolboy with congenital heart disease, i.e., isthmus stenosis with an enormous heart; the volume was 1,800 c.c., i.e., 930 c.c. per m^2 of body surface. There was no congestion anywhere. His venous pressure was 9 cm. At that time he still had a good reserve of strength, and performed even the severest functional test without difficulty. He played football without becoming breathless. Circulation time: first taste sensation at 20 seconds, maximum at 40 seconds, and cessation of taste sensation after 60 seconds. This case, in which congestion was entirely absent, was an excellent example of the fact that prolongation of the circulation time is determined by the degree of cardiac dilatation, i.e., by the amount of residual blood.

CASE 3.—The patient was a 45-year-old lift attendant who, for twenty-seven years, had had rheumatic mitral disease. Beginning in 1924, he had been a patient on many occasions at a number of hospitals in Stockholm, including the Sabbatsberg Hospital in 1940. After 1933 the heart volume increased enormously. On his admission to the Sabbatsberg Hospital, in 1940, remarkably enough there was no edema.

His general condition was fair. He had no fever. The sedimentation rate was 26 mm. in one hour. Physical examination showed no edema, but somewhat pronounced cyanosis of the face which increased on exertion. The liver was palpable two fingerbreadths below the costal arch (cardiac cirrhosis?). The blood pressure was 140/80, the vital capacity, 2,530, and the calculated vital capacity, 3,850.

The circulation time could not be measured with 5 c.c. of a 20 per cent decholin solution because the patient did not perceive any bitter taste. With 10 c.c. of a 20 per cent decholin solution, the first taste sensation was felt after 40 seconds. The taste sensation disappeared after 65 seconds.

Pronounced pulsations were visible over the precordia. The heaving apical impulse covered four fingerbreadths in the fourth intercostal space. Accentuated diastolic thrills were present over the lower left part of the thorax. Over the whole heart there was a long-drawn-out systolic murmur, with maximum intensity at the apex. At the apex, also, there was a long-drawn-out, rolling diastolic murmur. To the left of sternum a fairly long, rushing diastolic murmur was heard.

Roentgenologic examination showed that the heart was enormously enlarged, with pronounced pulsations all over. The total heart volume was 3,450 c.c., i.e., 1,740 c.c. per m^2 of body surface. There was moderately pronounced congestion of the lungs.

The electrocardiogram showed auricular fibrillation, with a ventricular rate of 90. T_1 was negative, and T_2 and T_3 were positive. QRS measured 0.09 seconds. The ventricular complexes were notched in all leads. Diagnosis: Auricular fibrillation, partial bundle branch block, and coronary insufficiency.

This case was remarkable in several respects. In the first place, I had never before seen such a large heart. Probably all the chambers of the heart were considerably dilated. Both the left and right auricles contributed very considerably to the enlargement, but it is extremely probable that, to a certain extent, the ventricles also participated. In the second place, the patient did not perceive any bitter taste with the ordinary amount of decholin, namely, 5 c.c., which every normal person and cardiac patient reacts to promptly. (It is naturally not ideal to use decholin as a test substance because the result depends on the sensation of taste.) In this case the explanation probably is that the large amount of residual blood diluted the decholin so much that no bitter taste was perceived. Not until twice the usual amount was given could the circulation time be measured, and then it was clearly prolonged; above all, the taste sensation was very protracted.

Study of these three cases of considerable enlargement of the heart, in which there were no insufficiency symptoms during rest (the venous pressure was practically normal, and there was no pulmonary stasis) shows clearly that the circulation time is determined not only by the degree of insufficiency and congestion, but also—and to a considerable extent—by the magnitude of the dilatation of the heart and, accordingly, the amount of residual blood, a circumstance to which attention has not been paid previously. It is not impossible, perhaps, in cases in which congestion is absent, to arrive at a conception of the degree of dilatation and the magnitude of the residual blood by means of measurements of the circulation time. An improved method for this purpose is being worked out, and experiments will be made to ascertain approximately the magnitude of the residual blood.

SUMMARY

The question whether the heart empties itself completely during systole has long been the subject of discussion. Everything indicates that

such is not the case, either under physiologic or—still less—under pathologic conditions.

Concerning the amount of blood which remains in the heart after systole, the so-called residual blood, extensive investigations have been made at the Seraphim Hospital and the Sabbatsberg Hospital. These investigations comprise (1) roentgenologic heart volume estimations under both physiologic and pathologic conditions, (2) post-mortem roentgenologic volume estimations, (3) post-mortem estimations of the heart volume by the displacement method, and (4) measurements of the capacity of the cavities. By this means, and with the help of circulation time measurements on patients with congestive heart failure and other patients with dilatation of the heart, but no failure, the amount of residual blood during life has been calculated approximately.

These investigations have shown:

(1) That, under both physiologic and pathologic conditions, the roentgenologic heart volume is subject to considerable changes which are due to variations in the amount of residual blood.

(2) That, with the help of ante- and post-mortem roentgenologic heart volume estimations, displacement estimations of heart volume, and measurement of the capacity of the cavities, it is possible to calculate approximately the residual blood during life. In certain cases the amount of residual blood during life may be quite large.

(3) That prolongation of the circulation time is not only an expression of congestive failure and retarded circulation—as has been generally considered—but is also, and largely, an indication of the amount of residual blood.

A method is being worked out for measuring the residual blood in vivo.

REFERENCES

1. Beneke, F. W.: Ueber das Volumen des Herzens und die Weite der Arteria pulmonalis und Aorta ascendens in den verschiedenen Lebensaltern, Schrift. d. Gesellsch. z. Beförderung d. gesamten Naturwissenschaften zu Marburg, suppl. 2, 1879.
2. Müller, Wilh.: Die Massenverhältnisse des menschlichen Herzens, Hamburg and Leipzig, 1883.
3. Henle, J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, 1866.
4. Kahlstorf, A.: Ueber eine orthodiagraphische Herzvolumenbestimmung, Fortschr. a. d. Geb. d. Röntgenstrahlen. **45**: 123, 1932.
5. —: Möglichkeiten und Ergebnisse röntgenologischer Herzvolumenbestimmungen, Klin. Wchnschr. **17**: 223, 1938.
6. Nylin, G.: Physiology of Circulation During Puberty, Acta med. Scandinav. suppl. 69, 1, 1935.
7. Lysholm, E., Nylin, G., and Quarnå, K.: The Relation Between the Heart Volume and Stroke Volume Under Physiological and Pathological Conditions, Acta radiol. **15**: 237, 1934.
8. Liljestrand, G., Lysholm, E., Nylin, G., and Zachrisson, C. G.: The Normal Heart Volume in Man, AM. HEART J. **17**: 406, 1939.
9. Hiffelsheim, E., and Robin, Ch.: Sur le rapport de la capacité de chaque oreillette avec celle du ventricule correspondant, J. de l'anat. et physiol. norm. et pathol. de l'homme et des animaux **1**: 413, 1864.
10. Hochrein, Max: Untersuchungen am venösen Teil des Kreislaufes, Arch. f. exper. Path. u. Pharmakol. **124**: 343, 1927.

11. Rollett, A.: Physiologie der Blutbewegung, Hermann's Handb. der Physiologie **4**: 148, 1880.
12. Chauveau, A., and Faivre, J.: Nouvelles recherches expérimentales sur les mouvements et les bruits normaux du coeur envisagés au point de vue de la physiologie médicale, Gaz. méd. de Par. **365**: 406, 569, 1856.
13. Roy, and Adami, J. G.: Remarks on Failure of the Heart from Overstrain, Brit. M. J. **2**: 1321, 1888.
14. Starling, E. H.: The Linacre Lecture on the Law of the Heart, London, 1918.
15. Nylin, G.: The Relation Between Heart Volume and Stroke Volume in Recumbent and Erect Positions, Scandinav. Arch. f. Physiol. **69**: 237, 1934.
16. Jonsell, S.: A Method for the Determination of the Heart Size by Teleroentgenography (A Heart Volume Index), Acta Radiol. **20**: 325, 1939.
17. Moritz, F.: Diskussionsinlägg vid Deutsche Gesellschaft für innere Medizin's kongress i Wiesbaden, 1935.
18. Binhold, H.: Über das Herzvolumen bei Emphysem, Asthma und Tuberkulose der Lungen, Ztschr. f. Kreislaufforsch. **27**: 145, 1935.
19. Kahlstorf, A.: Das Verhalten der Herzgrösse beim Herzjagen, Klin. Wchnschr. **15**: 1028, 1936.
20. Natvig, P.: The Volume of the Heart in Müller's and Valsalva's Tests, Acta Radiol. **15**: 657, 1934.
21. Böhme, W.: Über zwei neue, von der Respiration abhängige, klinisch erfassbare, röntgenologisch geklärte Herzphänomene, Fortschr. a. d. Geb. d. Röntgenstrahlen. **55**: 107, 1937.
22. Nylin, G.: Functional Heart Tests and Their Clinical Significance, Acta med. Scandinav. suppl. **78**: 64, 1936.
23. —: De kliniskt användbara hjärtfunktionsproven och deras betydelse, Nord. med. tidskr. **10**: 1737, 1935.
24. Liljestrand, G., Lysholm, E., and Nylin, G.: The Immediate Effects of Muscular Work on the Stroke and Heart Volume in Man, Scandinav. Arch. f. Physiol. **80**: 265, 1938.
25. Nylin, G., Sällström, Th., and Ågren, O.: Physiologische und pathologische Herzvolumenschwankungen, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **12**: 369, 1939.
26. Nylin, G.: Vitamin B_1-brist som orsak till hjärtinsufficiens, Nord. med. tidskr. **15**: 827, 1938.
27. Warburg, E.: Two Early Cases of Myxoedema Heart, Acta med. Scandinav. suppl. 59, 575, 1934.
28. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow, J. Clin. Investigation **4**: 389, 1927.
29. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**: 766, 1933.

RESTING PERIPHERAL BLOOD FLOW IN THE ANEMIC STATE

David I. Abramson, M.D., Sidney M. Fierst, M.D., and
Kamillo Flachs, M.D.
Cincinnati, Ohio

IT IS well known that patients with anemia, even of a severe degree, show very few signs of cardiac distress when at rest. Since the function of oxygen transport is affected by anemia, it would be expected that certain cardiovascular adjustments must take place in order to maintain an adequate supply of oxygen to the tissues. In this connection, Morawitz and Röhmer[1] found that venous blood from resting patients with anemia had an oxygen saturation of only 15 to 50 per cent, as contrasted with 60 to 75 per cent in normal blood; this suggested that a greater than normal dissociation of oxygen from the hemoglobin takes place under these circumstances. Further, a number of investigators have noted a moderate augmentation of cardiac output[2-6] and a reduced arm-to-tongue circulation time;[6, 7] these observations constitute indirect evidence for the view that there is also an increased rate of blood flow in anemia. In contrast, Stewart,[8] using the calorimeter, found a diminished circulation in the hand in this state, and Fahr and Ronzone[3] noted many contracted cutaneous capillaries in the fingertips. According to the latter investigators, part of the oxygen supply to the tissues may be obtained by shifting of blood from the skin to other areas, where the metabolism is more active.

Since no adequate quantitative study of the peripheral circulation in human subjects with anemia has been reported, it was thought worth while to apply the venous occlusion plethysmographic method to this problem.

METHOD

Eleven anemic patients with no complicating factors, such as organic heart disease, were studied. The type and cause of the anemia and the degree of deficiency in the erythrocyte count and hemoglobin content differed in the various subjects. Only 2 were less than 50 years of age, and 7 were above 60. Blood flow measurements, in c.c. per minute per 100 c.c. of limb volume, were generally made simultaneously upon the two upper extremities; the technique employed was identical in all respects with that previously reported.[9] The temperature of the water in the plethysmograph was maintained at 32° C., and the room temperature varied between 25° and 27° C. Fifteen to 20 readings were made after the patient had become accommodated to the environment and all psychic stimuli had been minimized. The pulse rate and blood pressure were ascertained in each experimental period.

From The May Institute for Medical Research, The Jewish Hospital, Cincinnati, Ohio.

Aided by the Samuel and Regina Kuhn Fund.
Received for publication July 2, 1942.

RESULTS

The results obtained were compared with those from a series of 25 normal persons of approximately the same age. The average control blood flow for the forearm was found to be 1.6 c.c. per minute per 100 c.c. of limb volume (σ – 0.3),* whereas that for the hand was 8.1 c.c. (σ – 3.5). Table I reveals that the forearm blood flow in 7 of the subjects with anemia was definitely increased; in 1 the readings fell within the higher range of the normal group; in 2 they were the same as the average of the controls; and, in 1 (L. Y.), the flow was below normal. The small flow in the case of subject L. Y. may be explained by the fact that he had been bedridden for many months. Patients M. S., C. B., and P. I. were examined on two occasions, and the readings recorded in Table I are the average of the different measurements. The average rate of forearm blood flow for the whole group of anemic patients was 2.5 c.c. per minute per 100 c.c. of limb volume, as compared with 1.6 c.c. for the normal subjects.

TABLE I

RATE OF RESTING BLOOD FLOW IN ANEMIC PATIENTS

SUBJECT	AGE	BLOOD FLOW IN C.C. PER MIN. PER 100 C.C. LIMB VOL.		B.P.	PULSE RATE	HGB. (GM.)	R.B.C.	REMARKS
		HAND	FOREARM					
M. S.	44	9.5	3.9	120/70		7.4	2.8 M.	Secondary anemia
L. Y.	74		0.8	106/50	72	8.4	2.8 M.	Debilitated
C. K.	68	3.3	1.7	120/74	84	7.25	2.23 M.	Acute bleeding; thrombocytes, 127,000
C. B.	59	6.2	2.0	96/56			2.9 M.	Bleeding peptic ulcer
A. L.	75	4.1	2.2	148/80		7.4	3.5 M.	
H. C.	24	5.5	3.8	110/60	92	9.6	3.0 M.	Banti's disease
A. B.	54	7.3	2.2	146/88	88	7.7	4.4 M.	Ca. of stomach
R. E.	72	11.1	3.3	200/60	105	6.8	4.5 M.	
A. K.	65	5.7	1.5	160/82	82	9.4	2.8 M.	Nutritional anemia ?
P. I.	63	3.8	2.3	158/88	72	7.6	2.8 M.	Pernicious anemia
H. F.	76		3.8	114/54	87	5.1	1.8 M.	Hemolytic anemia

As regards the circulation in the hand, the general trend appeared to be towards a somewhat decreased or low normal blood flow. Three patients had readings that were significantly less than normal, whereas those of the remaining six fell within the control range. The average for the group, as a whole, was 6.3 c.c. per minute per 100 c.c. of limb volume, as compared with 8.1 c.c. (σ – 3.5) for the normal persons. No distinct relationship appeared to exist between the degree of anemia and the rate of blood flow through either the hand or the forearm.

DISCUSSION

As previously stated, there is some evidence for the view that a greater than normal utilization of the arterial oxygen takes place in anemia.

*Standard deviation.

With respect to this hypothesis, Liljestrand and Stenström[4] have suggested that the ability of the tissues to obtain oxygen under the reduced tension that is present in the anemic state depends upon the opening up of new capillaries, with a consequent increase in the diffusion surface. However, there is a definite limit to the quantity of oxygen that can be made available through this means, for, the lower the hemoglobin content, the smaller will be the absolute amount of the gas which can be given off from each 100 c.c. of blood.

Increase in the cardiac output[2-6] and the tendency toward an augmented peripheral circulation through the forearm, as observed in the present study, constitute evidence for the view that another compensatory mechanism operates in the anemic state, namely, an increase in the rate of blood flow through the tissues. The relative decrease in the circulation in the hand cannot be interpreted as suggesting a shunting of blood from the cutaneous vessels to other vascular beds, for the blood flow in the hand is normally affected by many types of vasoconstricting stimuli.[10]

It would appear, therefore, that, in the anemic state, a normal oxygen supply to the tissues is maintained by both a moderate increase in the rate of blood flow and a greater utilization of the oxygen in the arterial blood. However, since these are the mechanisms called into play in the normal subject during muscular work, it is obvious that the cardiovascular system in the resting anemic subject is already geared to the equivalent of a higher level of effort, and hence even slight physical exertion may heavily strain its capacity.

SUMMARY

By means of the venous occlusion plethysmographic method, the peripheral circulation was investigated in a series of eleven patients with anemia of various types.

A moderate increase in blood flow was observed in the forearm, but in the hand the readings were, for the most part, within the lower range of normal or somewhat decreased.

The observations on the forearm constitute direct confirmation of the view that one of the compensatory mechanisms elicited in the anemic state is an augmented circulation through the tissues.

The authors wish to express their appreciation to Mrs. William Littleford for valuable technical assistance.

REFERENCES

1. Morawitz, P., and Röhmer, W.: Ueber die Sauerstoffversorgung bei Anämien, Deutsches Arch. f. klin. Med. **94**: 529, 1908.
2. Plesch, J.: Hämodynamische Studien, Ztschr. f. exper. Path. u. Therap. **6**: 380, 1909.
3. Fahr, G. E., and Ronzone, E.: Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias, Arch. Int. Med. **29**: 331, 1922.

4. Liljestrand, G., and Stenström, N.: Work of the Heart During Rest; The Influence of Variation in the Haemoglobin Content of the Blood Flow, Acta med. Scandinav. **63**: 130, 1925.
5. Richards, D. W., Jr., and Strauss, M. L.: Circulatory Adjustments in Anemia, J. Clin. Investigation **5**: 161, 1928.
6. Stewart, H. J., Crane, N. F., and Deitrick, J. E.: Studies of the Circulation in Pernicious Anemia, J. Clin. Investigation **16**: 431, 1937.
7. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies on Velocity of Blood Flow; Velocity of Blood Flow and Other Aspects of the Circulation in Patients With "Primary" and Secondary Anemia and in Two Patients With Polycythemia Vera, J. Clin. Investigation **9**: 679, 1931.
8. Stewart, G. N.: The Blood Flow in the Hands and Feet in Normal and Pathological Cases. Section IV. The Anemias. Harvey Lectures **8**: 113, 1912.
9. (a) Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, Am. Heart J. **17**: 194, 1939; (b) Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, Am. Heart J. **12**: 233, 1940.
10. Abramson, D. I., and Ferris, E. B., Jr.: Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli, Am. Heart J. **19**: 541, 1940.

THE RANGE OF THE NORMAL HEART IN ATHLETES

J. W. Wilce, M.D.
Columbus, Ohio

DISEASES and defects of the cardiovascular system seem to be the principal causes in total disqualifications for any military service.''[1]

In our war for survival, the serious analysis of all possible factors contributing to total rejection for active service and possible procedures for their correction seem fundamentally essential. Had I not held the deep conviction that my seemingly academic subject has very practical relationships to our present and future military efforts and general manpower conservation, I would not have prepared this paper.

Nationally speaking, many athletes who should furnish some of our best general military, officer, and aviation pilot material are being legitimately rejected from service for cardiac, as well as for many other medical and surgical, conditions. Broad participation in competitive athletics and strenuous recreative sport and physical education for practically all ages and both sexes is a definite and characteristic part of the life of our American democracy, but there is still a great deal to be learned concerning the cardiac effects of athletics.

Constant consideration of the many and varied medical aspects of exercise is appropriate, in order that its effects may be continuously constructive. Some of us have made investigations of certain parts of the field and much information has been acquired, but our knowledge is still incomplete. The Levine-Sosman group's continuing study of marathon runners and the Harvard Grant study seem particularly promising.

The essential background of the general athletic cardiac question is found in the following selected opinions. White says, ''Physical work and exercise do not cause heart disease, though they may precipitate or aggravate symptoms and signs of heart disease already present and *may temporarily exhaust the cardiovascular reserve even in a healthy individual.*''[2] Lewis states, ''Burdens imposed by physiological acts upon the *normal* heart, however heavy these burdens, may be said *never* to injure heart fibers, *never* to produce injurious dilatations, and *never to exhaust the heart's reserve.*''[3] Dublin, whose work on the longevity of college athletes is classic, states that ''Indulgence in athletics may in a good many instances have deleterious effects on the heart, especially if careful selection and supervision of athletes by trained men is not

From the Ohio State University.
Read at the Annual Meeting of the American Heart Association, Atlantic City, N. J., June 5, 1942.
Received for publication July 2, 1942.

available."[4] Cole states, "Our business is to look for cardiac defects and protect the defective heart. For the heart that has proven itself healthy we have no concern."[5] But what is a "healthy," so-called "normal" heart from the athletic standpoint?

PRESENT STUDY

The writer has made an investigation which was started to obtain evidence concerning the following postulates:

1. "Athletic heart," in the sense of a permanently enlarged, clinically inferior heart, does not exist in the absence of etiologic factors which are scientifically accepted as the cause of actual or potential cardiac disease.

2. *Under present conditions of American athletics,* many inferior or potentially inferior hearts of competing athletes may have their inferiority factor increased by athletic competition or by any degree of exercise which is too heavy for a particular person.

3. Certain so-called normal hearts may show relatively minor, transitory, physiologic size changes which have little, if any, practical clinical significance.

The present study gives objective data concerning the supposedly normal hearts of American athletes as they present themselves for health examinations.

The evidence submitted at this time is based primarily on a thirteen-year study of the history and cardiac size of 233 male American athletes whose ages ranged from 16 to 80 years; they were selected from 3,000 cases. The cases are well distributed up to the age of 50. The classification of "athlete" is based on my own judgment, after forty years of contact with the field in varying capacities.

TABLE I

AGE RANGE OF AMERICAN MALE ATHLETES

AGES	NUMBER IN GROUP	PER CENT
16-24	59	23.41
25-29	61	24.20
30-39	74	29.36
40-49	34	13.49
50-59	19	7.53
60-69	3	1.19
70-79	1	0.39
Over 79	1	0.39

METHODS USED

Orthodiagrams were made of the anteroposterior heart shadow in diastole during quiet respiration, in the upright position (as well as many "obliques" in questionable cases). The cardiac area was measured with a planimeter, after completion of the upper and lower borders. Area and diameter were ascertained, and percentages of the deviations from normal were computed according to the Hodges and Eyster postulated normal cardiac areas and diameters, based on age, height, and

weight, using the Kurtz nomogram, and checked with the cardiac slide rule. The size was also ascertained by the cardiothoracic ratio method of Danzer, but this was considered less accurate.

The study is secondarily a clear illustration of the great variation in the estimate of heart size by these methods.

Electrocardiograms, functional tests, and the essentials of physical examination were obtained in a large percentage, but not in all, of the cases.

In this study, plus 10 per cent is considered the upper limit of normal area; 0 per cent is the average normal of both area and diameter figures. The area method of judgment as to size was used primarily.

TABLE II

CARDIAC SIZE OF 233 AMERICAN MALE ATHLETES

	AGE	% DEVIATION AREA +	% DEVIATION AREA −	% DEVIATION DIAMETER +	% DEVIATION DIAMETER −	% C.T.R.
Means	32.6	17.75	8.01	9.5	6.51	48.89
Extremes						
a) Max.	80	65.5	27.8	41.2	28.47	66.6
b) Min.	16	0	0.8	0	0	38.7
Cases		177	77	161	93	254
Algebraic Mean of % Deviation		Areas 9.94+		Diameters 3.63+		

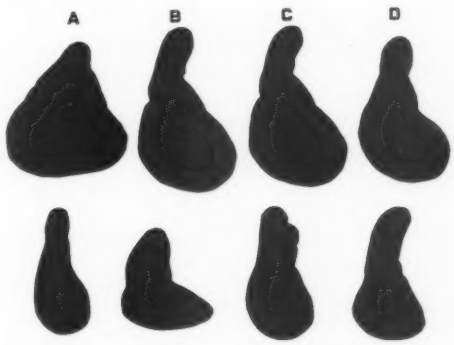


Fig. 1.—Maximum and minimum heart areas in study groups. *A*, 3000 athletes; *B*, athletic series, 233 persons. American male athletes; statistics in Table II; *C*, athletic series; "organic" or "marked inferiority factor" hearts; increased injury by athletics postulated: 25 subjects. See statistics in Table IV; *D*, "normal" hearts of 36 athletes. See statistics in Table III.

ARE ATHLETES' HEARTS NORMALLY ENLARGED?

The popular belief of laymen and many physicians is that the heart, like any other muscle, enlarges under conditions of work or exercise. *Athletes' hearts are not all enlarged; some are enlarged, some are normal, and some are small.* In my series the cardiac areas ranged from plus 65.5 per cent to minus 27.8 per cent. The algebraic mean of all

areas from 233 persons and 254 tracings was plus 9.94. One hundred thirteen of 233 hearts were absolutely enlarged, that is, larger than the *allowed normal* area range of 10 per cent above *average normal* (0 per cent). One hundred twenty were below this standard of normal size. Absolute enlargements exist, and would be called athletic hearts by some, but size increase may be explained by inheritance, disease, or deficiency factors before, during, or after active sport.

A few cases illustrating the present heart sizes of older athletes are presented in Fig. 2.

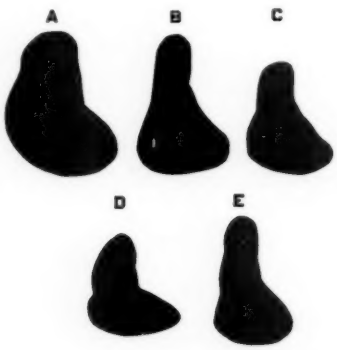


Fig. 2.—Athletes' geriatric aspects. Five cases illustrating present heart sizes of older athletes. (C.T.R. = Cardiothoracic ratio.) *A*, Aged 80 years, Ht. 73 inches, Wt. 206 pounds, area 49.6% plus, diameter 38.4 plus, C.T.R. 53.5%. *B*, Aged 56 years, Ht. 74 inches, Wt. 218 pounds, area 1.47% plus, diameter 6.61 minus, C.T.R. 46.6%. *C*, Aged 62 years, Ht. 66 inches, Wt. 174 pounds, area 11.92% minus, C.T.R. 54.3%. *D*, Aged 53 years, Ht. 68½ inches, Wt. 190 pounds, area 19.64 % minus, diameter 40.67 plus, C.T.R. 57.8%. *E*, Aged 55 years, Ht. 73½ inches, Wt. 179 pounds, area 27.8% minus, C.T.R. 42.8%.

A. Yale athlete. One of the earliest football and crew men, aged 80 years. Cardiac area 49.6 per cent plus deviation. This sportsman and golfer, forty years after college competition, gave a history of many potential heart disease factors, including diphtheria. Increased heart size is explainable as a result of disease plus sport factors. Although his heart was organically enlarged, his general constitutional strength made possible a long and useful life. Pneumonia was the cause of death.

B. One of Michigan's greatest Olympic track and football stars, thirty years after. Cardiac area showed a 1.47 per cent plus deviation.

C. Cornell and Pennsylvania athlete, aged 62 years, fine all-around athlete in college—baseball, football, track, sprinting. Practice of medicine and moderate recreative sports since. Excellent condition for age. Cardiac area showed 11.92 per cent minus deviation.

D. One of Colgate's greatest all-around athletes, Olympic track hurdle winner and All-American football player, thirty years after competition. Cardiac area showed a 19.64 per cent minus deviation.

E. Washington and Jefferson all-around athlete, aged 55 years. Cardiac area showed a 27.8 per cent minus deviation. This area was much below the average normal, in spite of the history of proved, early, organic rheumatic heart disease, with rheumatic fever three years before examination.

NORMAL CARDIAC VARIATIONS IN RELATION TO BODY HABITUS

The usual normal constitutional variations in heart shape are naturally also normal for athletes. The vertical cardiac position is less frequently seen than the oblique and lateral. An excellent illustration of this normal contrast is furnished by two Chicago University athletes twenty years after competition (Fig. 3). From personal knowledge, these were two of the best all-around athletes in the old days of Chicago's athletic superiority. They had approximately the same athletic experience, namely, football, basketball, baseball, and track, both in high school and college, approximately the same postgraduate exercise, and no recognizable potential or organic heart disease factors. There was much less than the usual degree of dental caries in both cases.

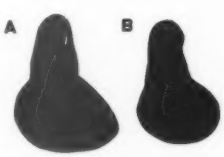


Fig. 3.

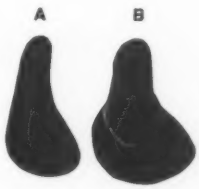


Fig. 4.

Fig. 3.—Normal body habitus and cardiac variations. *A*, Aged 42 years, Ht. 68 inches, Wt. 180 pounds, area 32.45% plus, diameter 23.86 plus, C.T.R. 59.2%. *B*, Aged 48 years, Ht. 73 inches, Wt. 180 pounds, area 12% minus, diameter 6.82 minus, C.T.R. 40.4%.

Fig. 4.—Twenty-year follow-up of two Wisconsin crewmen. *A*, Aged 37 years, Ht. 72 inches, Wt. 182 pounds, area 20.63% minus, diameter 10 minus, C.T.R. 48.1%. Normal heart. *B*, Aged 42 years, Ht. 74½ inches, Wt. 227 pounds, area 18.7% plus, diameter 12.5 plus, C.T.R. 52.7%. Deceased age 49. Lymphosarcoma.

Twenty years after competition, the heart area of the man of sthenic type showed a 32.45 per cent plus variation, whereas the area of the heart of the tall, coördinated, so-called true athletic type showed a 12 per cent minus variation. It is fair to say that the sthenic athlete had more natural energy. Both engaged in track sports and baseball in the spring, but the sthenic man had indulged in two-mile competition in a small quantitative degree, whereas the taller man had indulged in much less strenuous high jumping.

TWENTY-YEAR FOLLOW-UP STUDY OF TWO WISCONSIN CREW MEN

Two cases are presented (Fig. 4) as twenty-year "follow-ups"; these boys were in the Schumacher and Middleton[8] series at Wisconsin in the years 1912 and 1913. Both boys were excluded from crew work at that time because of enlarged hearts. Twenty years after the first examination, the heart of the first man (Case 14) was not enlarged and showed no evidence of disease. It is entirely possible, of course, that the heart was enlarged at the earlier time, and returned to normal when the lad was taken away from intensive activity. The heart may have been saved a longer period of enlargement by restriction in exercise.

The heart of the second man (Case 15) was entirely different. Twenty

years after the first examination it was enlarged, and the electrocardiogram showed an abnormal degree of left axis deviation. The basal metabolic rate at the time of my examination, in 1933, was –24 per cent. This man has not indulged in active recreative sport in the degree that might have influenced his heart size since graduation. I believe that this heart inherited a tendency to abnormality. The myxedema heart syndrome is possible in this case. Other inferiority factors, outside of a slight chronic sinus condition, played no part. I believe that this heart was enlarged at the time of the Wisconsin examination, but that it was even then a "hypothyroid heart," possibly exaggerated by high school athletic experience. This is purely an opinion. I knew the physical and personal characteristics of these men at the time of the Middleton examination.

It may be of significance that the lymphoid disease tendencies in Case 12 of my series have been confirmed; this man recently died at the age of 48 years from lymphosarcoma. I cannot correlate any athletic factor with his early death.

It was not until 1927 that the English translation by an outstanding internist, Louis M. Warfield, of *Heart and Athletics*, by Felix Deutsch and Emil Kauf, gave real support to the previously questioned presentation of Schumacher and Middleton.[8]

"STRICTLY NORMAL" ATHLETES' HEARTS

Strictly speaking, a normal, healthy heart is one which shows no evidence of organic disease, congenital or acquired, no abnormal variation in size or shape under accepted standards, no evidence of deficiency or degenerative conditions, no abnormal variation in functional efficiency, and no history of any condition which is known to predispose to heart disease or to favor it.

The most amazing thing to me in my entire study was that, by these present-day standards, *only twenty-nine hearts in my entire group of 233 cases were "normal."* If we omit from our definition "no abnormal variation in size or shape under accepted standards," thirty-seven were normal.

I have classified these thirty-seven athletes, who have competed intensively in American sport and qualified under the above definition of "strictly normal," as normal. They have never had organic disease, or any disease included in the army and navy lists or in the criteria for cardiac diagnosis as potential heart disease factors, namely, scarlet fever, chorea, diphtheria, measles, rheumatic fever, tonsillitis, influenza, typhoid fever, syphilis, gonorrhea, tuberculosis, or chronic focal infection.[6, 7] They are normal athletes, with absolutely normal function, so that athletics is postulated as the only possible influence on heart size. The evidence, that of their own histories, is limited in accuracy, as is all patient's testimony.

The range of normal of these hearts is shown in Table III. These

TABLE III

CARDIAC SIZE AMONG AMERICAN MALE ATHLETES; SPECIAL GROUP OF 37 CASES IN WHICH THERE WAS NO DISEASE (POSTULATED "NORMAL")

	AGE	% DEVIATION AREA +	% DEVIATION AREA -	% DEVIATION DIAMETER +	% DEVIATION DIAMETER -	% C.T.R.
Means	33.8	9.68	6.66	8.34	6.7	46.65
Extremes						
a) Max.	70	20.3	17.69	19.03	18.4	64.8
b) Min.	17	0.89	1.69	1.639	0	33.6
Cases		18	19	12	25	37
Algebraic Mean of % Deviations		Areas 1.29-		Diameters 1.82-		

CASE *	SIZE ORDER AREA	SIZE ORDER C.T.R. †	NAME	AGE	AREA % DEV. +	AREA % DEV. -	TRANS. DIAM. % DEV. +	TRANS. DIAM. % DEV. -	% C.T.R.
105	1	18	E. M.	26	20.3		8.53		45.7
45	2	7	R. E.	45	19.7		1.95		51.4
46	3	15	J. E.	31	17.93		1.561		47
71	4	6 (a)	W. H.	27	15.8		12.3		53
143 (b)	5	2	C. S.	32	15.26		12.98		56.4
130	6	5	C. P.	70	14.6		7.03		53.7
4	7	31	F. B.	29	14.5			14.4	33.6
143 (a)	8	3	C. S.	23	10.7		10.93		55.2
Hypothesized as Physiologic "Athletic" or "Work" Hearts									
188	9	6 (b)	S. W.	41	9.92		8.83		53
106	10	10	S. M.	32	9.91		7.2		50
151	11	23	M. S.	27	8.41		2.46		43.4
41	12	1	J. D.	49	5.1		19.03		64.8
146	13	11	C. S.	35	4.34			7.1	49.4
97	14	20	J. G. L.	38	3.57		1.639		43.7
55	15	14	J. G.	28	1.612			6.72	47.1
49	16	19	R. H.E.	35	0.926		0.847		43.9
147	17	9	H. S. S.	43	0.918			0	50.4
59	18	4	E. G.	39	0.893			7.26	54.5
32	19	28	C. C. C.	40		0.826		7.87	40.8
168	20	17 (b)	B. C. T.	17		1.69		1.6	45.8
164	21	29 (b)	F. S.	25		2.43		4.23	40.2
117	22	13	C. S. O.	24		2.479		0	48.1
66	23	29 (a)	A. H.	43		2.52		18.4	40.2
19	24	8	H. D. S.	35		2.9		5.41	50.7
155	25	24 (b)	O. B. S.	35		2.9		9.93	42.5
166	26	12	H. S.	35		3.64		3.97	49.1
192	27	25	H. W.	32		6.03		6.35	42.1
54	28	24 (a)	G. F.	24		6.37		.573	42.5
141	29	17 (a)	D. R.	28		6.45		12.68	45.8
193	30	27	W. W.	32		6.96		10.5	41.1
139	31	16	R. R.	27		7.62		1.502	46.3
65	32	24	P. G.	26		8.7		8.94	43
125	33	30	D. P.	33		9.92		6.3	39.6
112	34	22 (b)	B. M.	33		9.92		13.62	43.5
131	35	26	M. P.	24		10.43		11.81	41.5
102	36	21	B. M.	40		17.69		7.9	43.6
31	37	22 (a)	E. C.	49		17.1		5.425	43.5

*Individual cases have numbers. Cases such as 143 are lettered (a) for first examination, and (b) for second examination, etc.

†Letters following numbers signify, for example, that Case 71 has sixth largest C. T. R., noted as 6 (a). Case 188 had the same C. T. R., is also sixth in C. T. R. size order, but is given order number 6 (b) to differentiate.

areas range from deviations of 20.3 per cent plus to 17.69 per cent minus. The algebraic mean area was 1.29 per cent plus, against a postulated upper limit of normal of 10 per cent plus. The algebraic mean diameter was 1.82 per cent minus.

Since no Wassermann reactions, vitamin B deficiency tests, or basal metabolism measurements were done, it is not claimed that this evidence is conclusive. Clinical inspection showed no evidence of hypothyroidism. Compared to some investigations of the subject in the past, from which many have generalized, this examination is relatively satisfactory because the vitamin B and metabolism deficiency influences on the size of the heart were not known twenty-five years ago, and their potential influence is still very incompletely considered.

Granting, for the moment, that the possible error of omission was not actual, *seven of the thirty-seven hearts which were postulated as normal were enlarged by athletic competition, and would qualify as true athletic or work hearts, or normal hearts physiologically enlarged by exercise.* These hearts were absolutely normal clinically and functionally. The eventual significance of their enlargement is unknown. According to my belief, they are normal for all practical purposes, and will permit a normal or greater than normal life expectancy.

DAMAGED HEARTS AND ATHLETICS

The second postulate is "under present conditions of American athletics *many* athletes with organic or inferior value or potentially inferior value hearts compete." The abnormalities of such hearts may be, and often are, increased by athletic competition or any excessive degree of exercise. What present-day conditions in American sports[10-11] are pertinent to our discussion?

Many athletes compete in American sports today who should not be allowed to do so, medically speaking, for the following reasons:

1. No pre-sport examination. This condition does not exist in the better colleges, but 28 per cent of 9,000 college freshmen testified to this situation in their high school and earlier experience.

2. Inadequate pre-sport history or examination, and omission, in many instances, of any medical opinion before return to sport after illness.

3. Lack of accepted medical standards for participation in various types of sports.

4. Personal neglect of the doctor's order because there is a tremendous psychologic, physical, and social satisfaction in sports.

5. Desire of parents who want the thrill and secondary advantage of their sons' athletic prowess.

6. Public opinion and pressure on athlete and doctor to allow good athletes to compete.

7. Occasional political, instead of educational, sports and recreational administration.

8. Great public recreational systems in which players are allowed to compete intensively without medical examination of any kind.

9. The prevalence of informal "sandlot" type competition, with no formal medical "participation control."

10. The national tendency to promote team competition for "grade schoolers" without adequate medical guidance.

11. Sports articles in popular magazines which occasionally promote the public acceptance of "half truths" concerning the medical effects of sport.

Many athletes are denied participation in American sports who should be allowed to compete for the following reasons:

1. The medical viewpoint of what constitutes the proper medical standards for participation in various sports varies a great deal.

2. Many boys are excused from sport because of a "murmur," although certain leading cardiologists and other physicians allow persons with small degrees of chronic valvular involvement certain degrees of participation.

3. Cases need individualization in the light of relative evaluation of social, economic, and psychologic values, as balanced against possible medical injury through participation.

The lay viewpoint of this whole question of the effect of athletics on the heart is influenced by newspaper reports such as the following:

BOY HITS HOMER, RUNS BASES, DIES

Bellefontaine, O., May 7.—(A. P.)—J. E. D., 13, hit a home run in a school baseball game today, circled the bases, and fell dead. Physicians blamed heart disease.

SICK RUNNER IS VICTORIOUS

Boston, April 20 (A. P.).—Students of long-distance running today were asking themselves just what J. S., the National A.A.U. marathon champion, would have done to the Boston A.A.'s Blue-Ribbon field if he really had felt fit.

The 27-year-old Medford milkman, so weakened by a recent influenza attack that he did not believe he could go more than 15 miles, yesterday clipped one minute, thirty-seven and two-fifths seconds off the famed Hopkinton-Boston course record, while outdistancing the closest of his 113 rivals by more than a quarter-mile. His time for the 26-mile, 385-yard classic was two hours, twenty-six minutes, fifty-one and one-fifth seconds.

It is logical to assume that a moderately damaged heart might be stronger than normal at some time before decompensation.

The volume, *Nomenclature and Criteria for the Diagnosis of Diseases of the Heart*, carries this pertinent example under Therapeutic Classification: "The functional capacity of the patient does not always determine the amount of activity which is permitted. For example, a child with active rheumatic carditis may not experience discomfort in playing baseball yet the physician knows that rest in bed is imperative."[9] Many athletes compete under this principle with less extreme medical conditions. These athletes are normal from the lay standpoint, regardless of the possible eventual bad effects of competition.

The capacity of some diseased or inferior hearts to take punishment in sport or work is tremendous. That is the reason so many athletes are considered normal when careful medical examination or post-mortem study after suicide or accident reveals organic changes in the heart valves, muscle, or pericardium before the heart had lost enough of its functional power to be noticeable to the public, athlete, coach, or trainer.

Data on the diagnosis of generalized enlargement of the heart in athletes (athlete's heart), without analysis as to cause, are given in Table IV.

TABLE IV

CARDIAC SIZE AMONG AMERICAN MALE ATHLETES; SPECIAL GROUP OF ABNORMAL HEARTS (DISEASE PRESUMABLY RELATED TO ATHLETICS)

		% DEVIATION AREA +	% DEVIATION AREA −	% DEVIATION DIAMETER +	% DEVIATION DIAMETER −	% C.T.R.
Means	24.2	28	1 case only	15.08	7.24	51.48
Extremes						
a) Max.	41	65.5	9.26	41.2	12.3	66.4
b) Min.	16	4.1	9.26	0.782	0.826	40
Cases	29	28	1	26	3	29
Algebraic Mean of % Deviations		Areas 26.73+		Diameters 12.77+		

CASE	SIZE ORDER AREA	SIZE ORDER C.T.R.	NAME	AGE	AREA % DEV. +	AREA % DEV. −	TRANS. DIAM. % DEV. +	TRANS. DIAM. % DEV. −	% C.T.R.
230 (a)	1	10	R. W. M.	32	65.5		36.2		55.4
219	2	2	V. W. E.	19	54.3		41.2		66.4
230 (b)	3	4	R. W. M.	34	52.6		33.62		59.1
221	4	11 (a)	G. E.	21	48.6		22.5		53.3
224 (b)	5 (a)	5	M. F.	24	41.1		30.0		56.2
225	5 (b)	3	H. F.	21	41.1		16.54		61.5
220	6	12	M. E.	29	40.7		26.8		55.5
238	7	13	H. M. S.	23	40.5		7.58		50.3
235	8	11 (b)	H. S.	23	37.6		5.35		53.3
232	9	8	F. P.	37	36.2		26.6		56.0
231	10	18	C. P.	17	33.3		19.67		47.9
215 (c)	11	14	H. B.	16	31.2		11.88		51.1
227	12	19 (a)	H. P. H.	28	30.1		13.56		47.8
224 (a)	13	6	M. F.	22	30		23.6		58.2
218	14	23	C. R. C.	34	28.3		11.4		45.0
223	15	19 (b)	R. F.	20	25.9		9.6		47.8
233	16	16	W. W. R.	23	25.4		8.89		51.5
237	17	20 (a)	C. S.	23	24.56		6.4		47.6
239	18	21	R. S.	28	24.35		4.03		47.2
236	19	24	B. S.	18	21.36		1.82		43.5
228	20	22	H. K.	23	20.83		9.09		45.5
226	21	20 (b)	H. C. G.	23	14.9		3.96		47.6
215 (b)	22	17	H. B.	16	12.84		0.848		48.5
222	23	20 (c)	P. A. E.	23	10.09			0.826	47.6
217	24	1	R. C.	41	8.26		14.3		66.6
215 (a)	25	15	H. B.	16	8.2		5.9		51.0
216	26	26	L. C.	21	6.96			12.3	39.0
229	27	9	H. J. K.	18	6.67		0.782		52.8
234	28	25	C. R.	29		9.26		8.62	40.0

For explanation of (a), (b), (c) see footnotes, Table III.

This is the group in which active participation in sport has been preceded, accompanied, or followed by significant organic or potential heart disease. The maximum deviation in the frontal heart area of this group is 66 per cent plus, and the minimum is 9 per cent minus. The algebraic mean area is 26.73 per cent plus, and the diameter, 12.77 per cent plus.

Every person in this series was *normal from the viewpoint of the trainer or layman.* All of these boys and men are getting along perfectly well and successfully indulging in various degrees of recreative and competitive physical activity. The interpretation as "normal" of all who can successfully engage in practical competition without dropping dead is widely accepted. *This makes for much misunderstanding between laymen and those physicians who try to practice preventive medicine.* Attempts to avoid the common cardiac neuroses must naturally also be a part of preventive medicine.

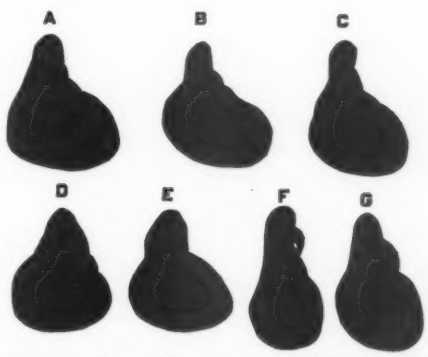


Fig. 5.—Radically organic heart disease in competing athletes. Athletic exaggeration of condition postulated. *A*, Aged 37 years, Ht. 5 feet 6½ inches, Wt. 160 pounds, area 84.26% plus, diameter 39.68 plus, C.T.R. 66.9%. *B*, Aged 18 years, Ht. 5 feet 11 inches, Wt. 183 pounds, area 50% plus, diameter 33 plus, C.T.R. 62%. *C*, Aged 21 years, Ht. 5 feet 7½ inches, Wt. 142 pounds, area 65.42% plus, diameter 32.45 plus, C.T.R. 61.5%. *D*, Aged 17 years, Ht. 67½ inches, Wt. 114 pounds, area 57.28% plus, diameter 41.12 plus, C.T.R. 66.7%. *E, F, G,* Other cases.

ILLUSTRATIVE CASES

A. A 37-year-old man with chronic rheumatic heart disease, area enlargement of 85 per cent plus, and auricular fibrillation, played thirty-six holes of golf a day on a hilly course before I saw him. He later bowled as many as fifty match games daily. I saw him two years after his first visit. His hypertrophy was reduced to 56 per cent plus after marked reduction of exercise (and happier marriage). His auricular fibrillation persisted (no deficit), and he was about to bowl three events in the American Bowling Congress at the time. In the lay mind, he was entirely normal for such activity.

B. Very marked aortic regurgitation, with marked left ventricular enlargement, was found in the case of a surprised boy, immediately after "all city" high school all-sports competition in Ohio's largest city school system.

C. A college freshman with chronic rheumatic mitral disease, a cardiac area showing a 65 per cent plus enlargement, and normal function was "normal" for all high school sport and freshman football before his disease was discovered. He played in high school and started to play in college with the consent of his family physician and of his father.

D. A boy with active rheumatic carditis and mitral disease was picked up by chance while competing in intramural athletics.

An exceptionally strong, well-endowed man, because of his high natural endowment, may perform normally in strenuous activity in spite of organic disease or handicap. A normal performance for the athlete with relatively great resistance and endowment is vastly different from that of the normal heart of an average man for average activity.

Degree of infection depends on the number and virulence of organisms and body resistance. Normal heart function and what a person may do with immediate or eventual safety depend on the degree of heart disease as related to constitutional strength, habitus, and endocrine and general organic make-up. In the cases noted above, and in many others which could be cited, the heart was normal for the degree of competition indulged in only in the light of the above formula. They were not cases of healthy hearts.

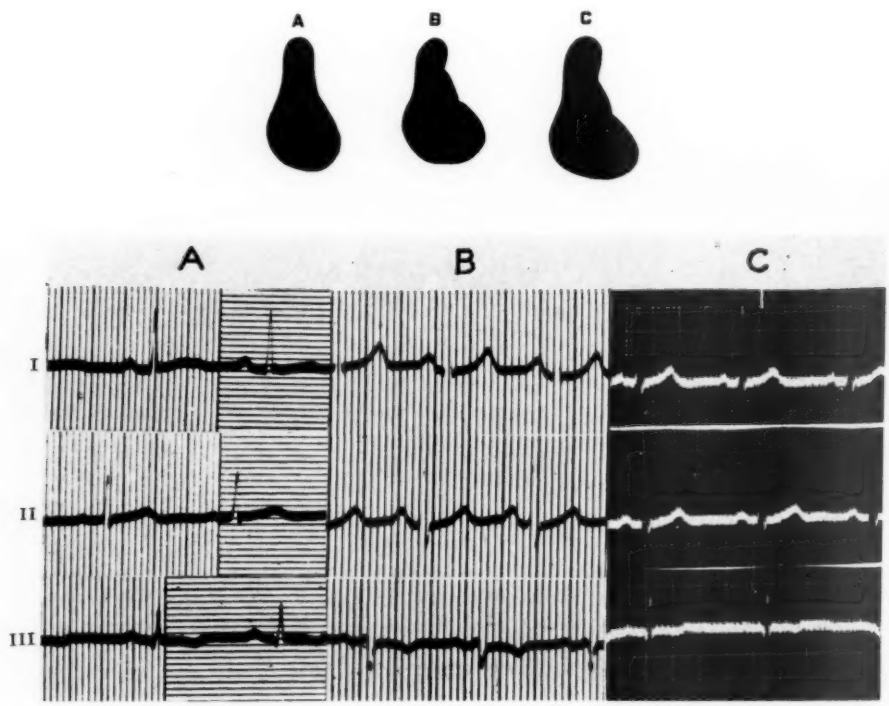


Fig. 6.—Heart size changes postulated as physiologic. Olympic sprint champion. *A*, Aged 22 years, Ht. 71½ inches, Wt. 152 pounds, area 15.38% minus, diameter 5.04 minus, C.T.R. 47%. *B*, Aged 24 years, Ht. 71½ inches, Wt. 162 pounds, area 9.3% minus, diameter 0.8 minus, C.T.R. 49.1%. *C*, Aged 26 years, Ht. 71½ inches, Wt. 157 pounds, area 3.3% minus, diameter 13.11, C.T.R. 50.9%.
Note left axis deviation in electrocardiogram, with return to normal in electrocardiogram *C*.

The writer originally suggested the appropriateness of using a clinical diagnostic phrase to describe such hearts as Cases 1, 2, and 4, as "rheu-

matic athletic," etc.,[12] including athletics as a contributing etiologic factor. Case 1 (upper left) and other cases in which competition in sports was thought to have increased the already existing abnormality are shown in Fig. 4.

PHYSIOLOGIC CHANGES IN THE SIZE OF THE HEART

The third phase of our thesis is that certain so-called normal hearts may show relatively minor, transitory, physiologic changes in size which have little or no practical significance.

The heart of an Olympic champion sprinter, under especially strenuous, pre-tryout, meet-training conditions, made necessary by injury, changed in area and contour and showed transitory left axis deviation in the electrocardiogram. Two years after discontinuing Olympic training, his heart showed an additional, slight increase in size, with only recreative sport and running, possibly because of the pre-Olympic strain. It was still not absolutely enlarged (see Fig. 6).

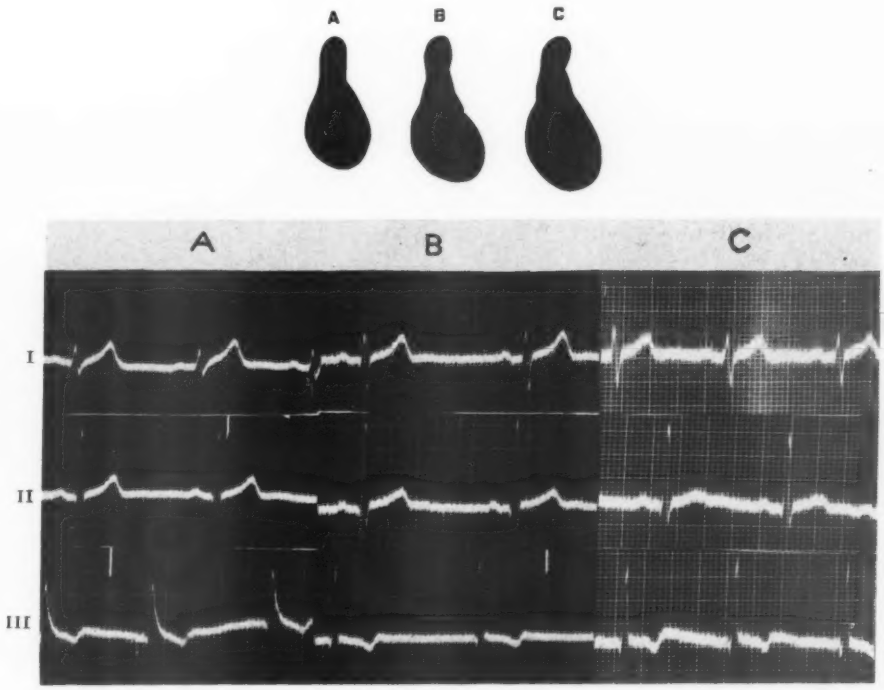


Fig. 7.—Heart size changes postulated as physiologic. High school tennis, basketball star. *A*, Aged 15 years, Ht. 75 inches, Wt. 150 pounds, area 20% minus, diameter 9.48 minus, C.T.R. 39.6%. *B*, Aged 16 years, Ht. 75 inches, Wt. 150 pounds, area 1.6% minus, diameter 5.17 minus, C.T.R. 40.5%. *C*, Aged 17 years, Ht. 76 inches, Wt. 170 pounds, area 3.7% plus, diameter 6.5, C.T.R. 42.6%.

The heart of a high school basketball star was examined over a period of three years; it gradually increased in size, but was still not absolutely enlarged. He is now a star at Notre Dame (see Fig. 7).

PATHOLOGIC CHANGES IN THE SIZE OF THE HEART

A high school coach brought in his star basketball player, who had been, in my opinion correctly, ruled out of competition by a local physician. The boy insisted that he would play anyway on an independent team, and therefore was given permission to play part time with the high school. He was seen three months later at the start of the basketball season. Much to my surprise, the coach had decided to "build the boy up and condition him" on his own responsibility. He had sent the player through strenuous practices, although allowing him participation in only alternating quarters, as agreed to previously. The boy's cardiac area had increased from 12.84 per cent plus to 31.2 per cent plus in three monhts, as illustrated by Fig. 8.

Fig. 8.—Heart size changes postulated as pathologic. *A*, Aged 16 years, Ht. 68 inches, Wt. 145 pounds, area 12.84% plus, C.T.R. 48.5%. *B*, Same. Three months later. Area 31.2% plus, C.T.R. 51.1%.

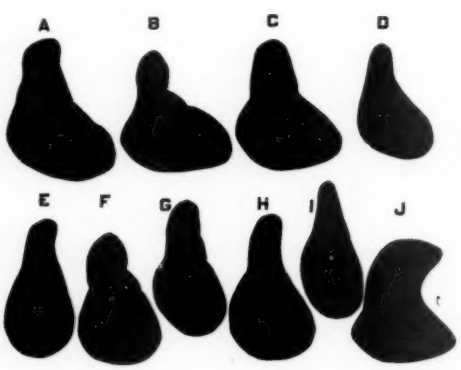


Fig. 9.—"Athletic hearts" as diagnosed by various physicians.

HEART	AGE	HT. INCHES	WT. POUNDS	AREA %	DIAMETER %	% C.T.R.
A	48	73	225	30.3 plus	21.35 plus	59.0
B	26	71½	210	25.2 plus	17.6 plus	63.01
C	52	68	190	21.55 plus	13.04 plus	59
D	17	62	128½	12.84 plus	0	48.5
E	22	73	160	9.83 plus	5.74 minus	43.4
F	23	73½	164	6.45 plus	4.07 minus	44.9
G	22	68½	142	1.83 plus	4.27 minus	42.1
H	38	71	169	0.84 minus	0	46.0
I	20	60	130	1.83 minus	12.05 minus	45.7
J	55	74	217	2.26 minus	17.22 plus	54.5

"ATHLETIC HEARTS" AS DIAGNOSED BY CERTAIN PHYSICIANS

The following points developed in the course of this study.

1. Some physicians, particularly general practitioners, still make the

diagnosis of "athletic heart" with a wide range of meaning, as shown by Fig. 9 in the case of ten of the fifteen hearts so designated. They ranged in area from a deviation of 30.3 per cent plus to 2.26 per cent plus, and from a small, vertical heart, to one with a cardiothoracic ratio of 54.5 per cent and "aneurysmal" dilatation of the aortic arch.

The diagnosis of "athletic heart" is not uncommon, as evidenced by the fact that fifteen in 3000 cases is 0.5 per cent, and that this is essentially the frequency of the diagnosis of active tuberculosis among college students. It should also be noted that the diagnosis of "athletic heart" is more generally socially acceptable than the diagnosis of tuberculosis or syphilis. It may even carry prestige in some circles.

2. It is apparently "normal" for the hearts of successful American Olympic team wrestlers and their alternates to average 26 per cent plus in cardiac area two days after successful final tryouts. Ten of thirteen hearts were increased in size. All but one had potential heart disease factors, and one had right-sided cardiac dilatation. The cardiac enlargement may have resulted partially from heavy fluid intake after temporarily breaking training, with its excessive dehydration incident to reducing to lower weights.

MILITARY ASPECTS

This study does reveal definitely the fact that there are many injured hearts among athletes before, during, and after competition. This fact may explain military rejections of athletes who are popularly considered normal. It is natural for a layman to hold the opinion that athletes are rejected from military service because of "athletic heart," but this is not the case. They are rejected because of organic heart disease of varying degree.

If military standards of heart size alone, without other evidence of cardiac abnormality, were strictly adhered to, some athletes would not be accepted for military service. My personal feeling is that every one of them, except those with definitely organic disease, could be accepted and would perform in a normal, and perhaps above normal, way in military service. The most practical aspect is the possibility that these hearts, whether physiologically or potentially pathologically enlarged, are not as acceptable for aviation at the higher flying levels.[13] This needs further investigation because Wearn[14] and others have shown that increase in cardiac size through hypertrophy of muscle fibers is not accompanied by an increase in the number of blood vessels, and therefore constitutes a relative inferiority under conditions such as altitude flying, which necessitates the best possible oxygen supply and utilization. Theoretically, oxygen debt would occur relatively earlier in hearts such as these. In cases of pathologically and potentially pathologically enlarged hearts, cardiac anoxemia would develop earlier than it would in cases of supposedly physiologic cardiac enlargement. These theoretical

considerations may be far outweighed by other intangible factors frequently found in true athletes, such as superior volitional trends and superior competitive spirit.

SUMMARY AND CONCLUSIONS

1. An analysis has been made of cardiac size by comparing orthodiagraphic areas and cardiac diameters with the Hodges-Eyster normal standards in a series of 233 persons selected from 3000 American male athletes. Conclusions from this study follow.

2. Generally, athletes' hearts are larger than nonathletes' hearts.

3. "Nonorganic cardiac enlargement" is probably of little clinical importance, and should be considered normal for athletes. Moderate variations from the *average* heart size in normal athletes, in the absence of other signs of organic heart disease, is of no particular significance. The eventual result of "nonorganic enlargement," however, is not as yet definitely known.

4. According to published standards of heart size, the hearts of many athletes are enlarged.

5. The hearts of persons of "softer type" may change size under athletic strain.

6. It is probably detrimental to the health of persons with organic heart disease to participate in sports.

7. The intangible advantages of true athletic training probably outweigh the disadvantages of moderate, "nonorganic" cardiac enlargement (granting that it does exist); this is important in deciding whether or not athletes are acceptable for aviation or other military service. Such hearts should be considered normal.

8. Participation in sport should be encouraged in every way, but only under alert, accurate, and liberal medical supervision.

REFERENCES

1. Rowntree, L. G., McGill, K. H., and Folk, O. H.: Health of Selective Service Registrants, J. A. M. A. **118:** 1224, 1942.
2. White, P. D.: Heart Disease, New York, 1931, The Macmillan Co., p. 442.
3. Lewis, Sir Thomas: Diseases of Heart, New York, 1933, The Macmillan Co., p. 154.
4. Dublin, Louis I.: Longevity of College Athletes, Harper's **157:** 228, July, 1928, (reprinted).
5. Cole, Norman B.: Present Day Opinion Regarding the Relationship Between Athletes and the Heart, Am. Phys. Ed. Rev. **33:** 571, 1928.
6. Reprint of Chapter II, Manual of Medical Department U. S. N., Government Printing Office, 1938, p. 1481.
7. Army Regulations 40-105, Government Printing Office, p. 19.
8. Schumacher, L., and Middleton, W. S.: Cardiac Defects of Immoderate College Athletics, J. A. M. A. **62:** 1136, 1914.
9. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York, 1940, New York Heart Association, p. 74.
10. Wilce, J. W.: Improved Health Standards for Athletics and Physical Education, Ohio State M. J. **34:** 171, 1938.
11. Wilce, J. W.: The Health of the High School Athlete, The Ohio High School Athlete—Official Organ of the Ohio High School Athletic Association **1:** 12, 1942.

12. Wilce, J. W.: Athletic Heart—Modern Conception and a Recent Investigation, Journal-Lancet **56**: 557, 563, 1936.
13. Wilce, J. W.: Aviation Medicine—A Defense Challenge to American Colleges and Universities (A Government Accepted Project), 1941, Ohio State University Press, p. 13.
14. Wearn, Joseph T.: Bulletin of the New York Academy of Medicine, 1941, p. 754.

DISCUSSION

DR. PAUL D. WHITE, Boston.—I would like to ask Dr. Wilce whether he believes that a possible factor of cardiac strain which will produce actual cardiac enlargement may be very strenuous effort during an illness. For example, a young football player may conceal an acute respiratory infection, if he can, and engage in a very hard game; I would like to ask Dr. Wilce whether he thinks that such a circumstance may have a deleterious effect.

DR. J. W. WILCE, Columbus.—Thank you, Dr. White, for asking that question, because it gives me a chance to bring out a point which was in my paper, but which I did not have an opportunity to discuss. I have several cases of that kind in my series.

You have in Boston the marathon runner who broke the record after he had just gotten out of bed with influenza. He thought he could run only fifteen miles, but he ran the twenty-five and broke the record. I hope that you will pick him up.

I saw a boy with influenza who was playing in a high school basketball tournament. I was able to get an electrocardiogram on him, and there was slight splintering of QRS_2. I have not had a chance to follow him up.

However, as a coach, twenty-four years ago, I sent a boy into a football game just after he had influenza. I was able to follow him twenty years later, and he did have a deep Q_2 and evidence of myocardial damage, with no other intervening disease factors.

DR. PAUL D. WHITE.—I have one other comment to make about which I have been in discussion with Dr. Wilce. He himself abstained from speaking of it.

A few weeks ago I received a letter from the *Journal of the American Medical Association*, asking for an answer to a query that has been raised as to the slowness of the heart rate in athletes. It was stated that reference had been made in some lay article to the fact that some mile runners, particularly Cunningham and MacMitchell, had pulse rates at rest that were under 40 normally, and the question was: "Is this possible?"

I had not encountered any normal person with a heart rate under 40, so I began to inquire of authorities, like Dr. Dill and Dr. Wilce, who have had rich experience. The answer from them was that they had not encountered any normal person, athlete or otherwise, with a heart rate under 40.

I pursued the point, and wrote to Cunningham and MacMitchell and got in touch with a few others. Dr. Robinson, who is at the Harvard Fatigue Laboratory, and is a former athletic trainer and a physiologist, sent me word that he had a graphic record of a two-mile runner whose normal resting heart rate had been recorded at 35.

Since then I have heard of three others. Although Cunningham has written to me that his heart rate has not been below 40 per minute so far as he knows, MacMitchell states that his pulse rate has been recorded at 32 at rest, one of the marathon runners, Kelly, has had a pulse rate of 38, and Dr. Graybiel has recently sent me the electrocardiogram of one of a thousand healthy aviators whom he studied last year which showed a heart rate of 38 at rest.

So, apparently, as in the case of almost all other rules, there are exceptions to this one, and it is really possible to have a normal pulse rate at rest, usually in an athletic person, under 40 per minute. I do not refer, of course, to the very slow heart rate which may be found in extreme inanition or starvation.

I am wondering if anybody else here has had any such experience.

DR. J. W. WILCE.—I was very much interested in your investigation of these distance runners. There was an article in the *Saturday Evening Post* in which a trainer said that this idea about distance running hurting the heart was a lot of poppycock.

I was going to show three hearts of distance runners who, although they were not definitely ill during the running, had such inferiority value factors at the time of their distance running that I certainly postulated bad effects from it. One had an anginal syndrome, one had early cor pulmonale, and the other had rheumatic heart disease.

I am interested in the type of highly specialized athlete that you mention as having an extremely slow heart rate.

The "amateur professionals" represent one very small group of athletes, the average amateurs represent an extremely large group, which includes almost everybody, and the professionals represent another. The closer one gets to the professional group, the more eventual effects one sees, because, obviously, with this group athletics are engaged in more intensively over a longer period of time. I believe that we should address ourselves primarily to those conditions that have to do with the great majority of the youth of the land, and that we should start to pay more attention to potential heart disease factors in diagnosis in the interest of prevention of cardiac injury from sports.

DR. PAUL D. WHITE.—I think we may all congratulate Dr. Wilce on at least the beginning of an attempt to solve a very difficult problem. This study presents further evidence that the normal heart has a wide range. As we have said before, we shall probably never be able to ascertain the exact limits of normal with any absolutely certain degree of accuracy.

EFFECTS OF CHANGES IN VENOUS PRESSURE UPON BLOOD FLOW IN THE LIMBS

CARL K. FRIEDLAND, M.D., JOHN S. HUNT, M.D., AND
ROBERT W. WILKINS, M.D.
BOSTON, MASS.

IT IS of considerable practical importance as well as of theoretical interest to know whether increasing the venous pressure in a limb by inflating a blood pressure cuff around it increases the blood flow in the limb. Linton, et al.,[1] at the 1940 meeting of this Section, reported that obstructing the venous outflow from the leg of the dog increased the blood flow through the femoral or iliac artery, as measured with the thermostromuhr. In similar experiments, but using the rotameter, Pritchard and his associates[2] found that blood flow decreased during the period of venous obstruction. We have studied the problem in human beings by four different methods, namely (1) capillary microscopy, (2) venous blood oxygen analysis, (3) skin temperature measurement, and (4) plethysmography.

CAPILLARY MICROSCOPY

The blood flow in the capillaries of the skin of the forearm and nail-fold was observed microscopically[3, 4] before, during, and after the inflation of a blood pressure cuff around the upper part of the arm to 30 and to 60 mm. Hg. A more objective index of the velocity of blood flow was obtained in some experiments by recording the time required for the gap between two columns of erythrocytes to pass from the arterial to the venous end of the capillary loop.

Twelve experiments were performed on nine normal subjects. Inasmuch as considerable spontaneous variation may occur in capillary blood flow,[4] at least ten observations were made at each congesting pressure. Confirming the reports of others,[4, 5, 6] it was noted that uniformly the rate of blood flow in a given capillary decreased upon inflation of the cuff. For example, in one experiment the time required for a gap to traverse the capillary loop was two, three, and seven seconds, respectively, during cuff pressures of 0, 30, and 60 mm. Hg. However, since it was also noted that during the inflation of the cuff many previously invisible capillaries came into view, the results of this method were not accepted as necessarily indicative of the blood flow to the limb as a whole.

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.
Presented at the annual meeting of the Section for the Study of the Peripheral Circulation of the American Heart Association, June 6, 1942.
Received for publication July 19, 1942.

VENOUS BLOOD OXYGEN ANALYSIS

Venous blood was drawn from the median cubital vein at a point on the forearm previously rendered anesthetic by the local infiltration of a 1 per cent procaine solution. The blood was taken in oiled syringes, fitted with needles which were filled to the tip with boiled, 30 per cent potassium oxalate solution (approximately 0.04 c.c.). It was then immediately transferred to a tube under freshly boiled, but cooled, mineral oil, where it was gently stirred to mix it with the anticoagulant. As quickly as possible, the oxygen content was determined in duplicate by the method of Van Slyke and Neill.[7] Two specimens of blood were obtained, one when there was no venous congestion, and the other at the end of ten minutes' venous congestion produced by inflating a cuff around the upper part of the arm to 60 mm. Hg. Eight experiments were performed on seven normal subjects. In four experiments the hand was excluded from the circulation by inflating a cuff at the wrist to 300 mm. Hg. Uniformly, the samples obtained during venous congestion contained less oxygen than the control specimens (Table I). Since

TABLE I

EFFECT OF VENOUS CONGESTION ON VENOUS BLOOD OXYGEN CONTENT

SUBJECT	VENOUS BLOOD OXYGEN CONTENT C.C. PER 100 C.C.	
	0 MM. HG	60 MM. HG
W. L.	12.21	4.42
	13.80	4.69
C. F.	7.13	3.03
	8.07	3.22
T. M.*	9.75	6.86
	10.81	7.12
H. C.	9.30	8.11
	9.62	8.52
C. O.	7.25	5.70
	7.33	5.74
C. R.*	8.86	6.63
	8.20	6.00
R. W.*	7.06	4.46
	7.00	4.85
	10.23	6.05
	10.60	6.05

*Hand circulation occluded.

Holling[8] has shown that, under resting conditions, changes in the oxygen content of the median vein blood reflect directly the changes in blood flow, the decrease in oxygen content during venous congestion was accepted as evidence of a decrease in blood flow.

SKIN TEMPERATURE

The temperature of the skin of the extremities was measured by thermocouples attached to the pads of the fingers and toes,[9] while the temperature of the room was kept as constant as possible. In some ex-

periments, arterial pressure, pulse rate, and rectal temperature were also measured. Twenty-six experiments were performed on eight normal subjects who lay supine in bed while the effects on skin temperature of inflating and deflating a blood pressure cuff above one elbow or knee were observed. The opposite limb served as a control.

When the body was exposed in a cool room, and the limbs were already cool as a result of sympathetic nervous vasoconstriction, venous congestion of one limb did not cause it to become warmer (Fig. 1, Table II). When the body was covered with blankets and heating pads, warm-

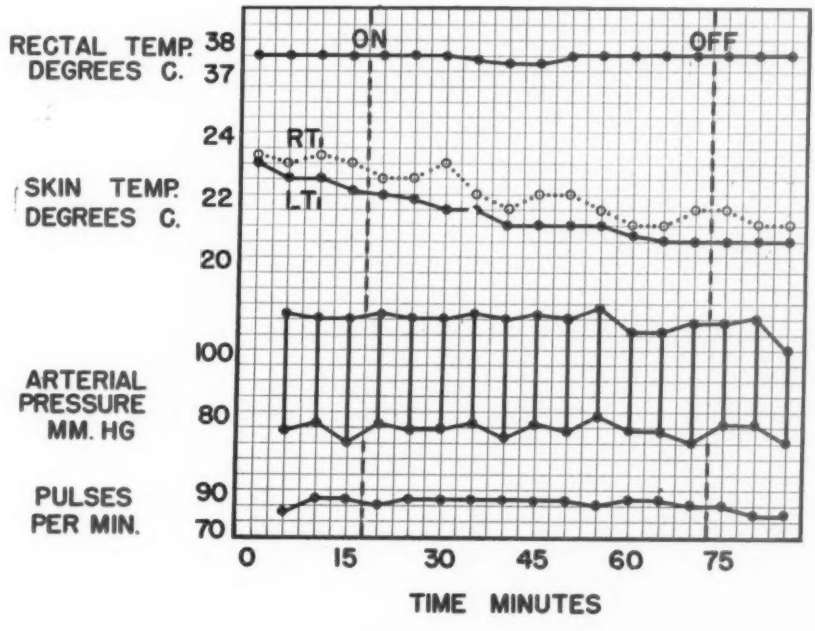


Fig. 1.—Effect of venous congestion upon cool extremities. Chart of rectal temperature; skin temperature of the right great toe (RT_1), and of the left great toe (LT_1); arterial pressure; and pulse rate during an experiment on a normal subject. At 17½ minutes (first vertical interrupted line) a cuff above the right knee was inflated to 50 mm. Hg. At 72½ minutes (second vertical interrupted line) the cuff was deflated.

TABLE II

EFFECT OF VENOUS CONGESTION (50 MM. HG) ON SKIN TEMPERATURE. SUBJECT COOL

SUBJECT	LEG CONGESTED	DURATION OF CONGESTION MINUTES	SKIN TEMPERATURE DEGREES C.			
			BEFORE		AFTER	
			RT_1	LT_1	RT_1	LT_1
C. F.	R	20	23.7	25.9	23.0	24.7
J. H.	R	40	24.5	24.0	24.6	25.3
A. P.	R	55	23.0	22.2	21.5	20.5
	R	65	21.5	21.0	21.1	20.8
M. C.	R	25	20.1	19.1	20.1	19.5
A. B.	L	10	24.1	24.0	24.1	23.7

TABLE III

EFFECT OF VENOUS CONGESTION (50 MM. HG) ON SKIN TEMPERATURE. SUBJECT WARM

SUBJECT	LEG CONGESTED	DURATION OF CONGESTION MINUTES	SKIN TEMPERATURE DEGREES C.			
			BEFORE		AFTER	
			RT_1	LT_1	RT_1	LT_1
C. F.	R	20	32.0	32.0	31.0	32.5
	R	20	34.6	34.5	34.0	34.5
	R	20	32.5	32.0	32.8	34.0
	R	30	34.6	35.0	34.0	35.5
J. H.	R	30	32.6	34.0	32.0	34.8
M. C.	R	25	34.5	34.7	33.0	34.8
A. P.	R	35	34.5	34.8	31.2	34.5
E. P.	R	35	35.0	35.4	35.4	36.0
A. B.	L	40	32.0	33.0	31.8	30.5
C. F.	L	25	35.1	35.5	35.1	35.0
R. W.	L	30	35.0	35.4	35.0	35.0
E. P.	L	30	34.3	35.0	35.5	35.0

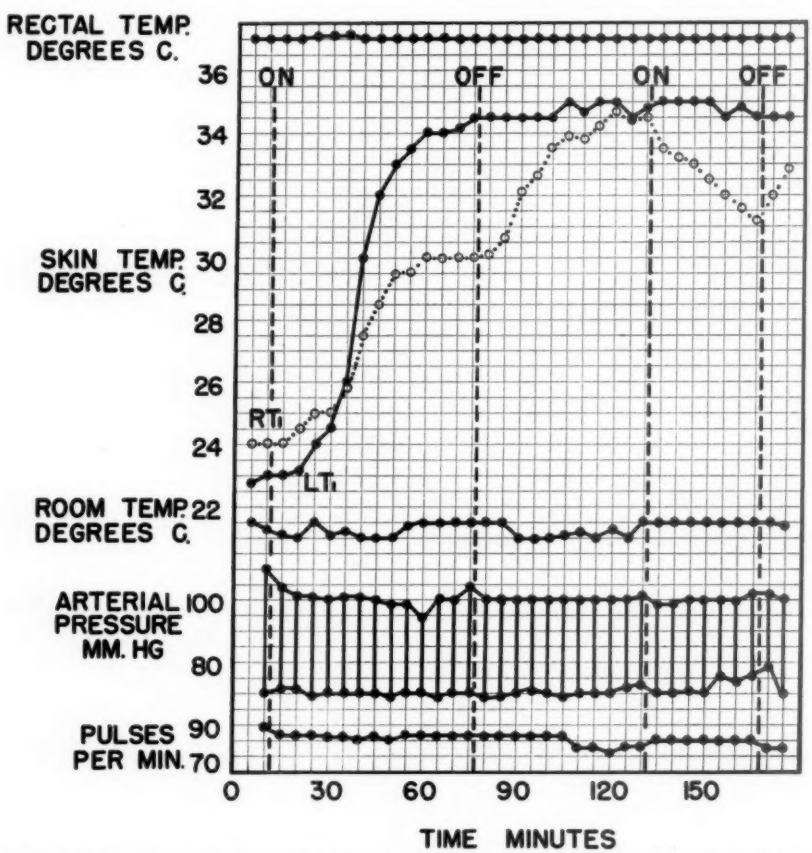


Fig. 2.—Effect of venous congestion upon warming of the extremities caused by sympathetic nervous vasodilatation. Chart of rectal temperature; skin temperature of the right great toe (RT_1), and of the left great toe (LT_1); room temperature; arterial pressure; and pulse rate during an experiment on a normal subject. At the beginning of the experiment the subject was covered with blankets and electric heating pads. At 12 minutes (first vertical interrupted line) a cuff above the right knee was inflated to 50 mm. Hg. At 77 minutes (second vertical interrupted line) the cuff was released; at 132 minutes it was reinflated, and, at 168 minutes, released.

ing of the extremities as a result of sympathetic vasodilatation occurred; this warming was not accelerated in a congested limb but, on the contrary, was retarded. Furthermore, the congested limb often failed to become as warm as the control limb, although, after release of the congesting cuff, it did become fully as warm as the opposite limb (Fig. 2). When both limbs were already equally warm as a result of sympathetic vasodilatation, venous congestion of one limb did not cause it to become still warmer, but, on the contrary, at times caused it to become somewhat cooler than the control limb (Fig. 2, Table III). In the same manner, while the body was being cooled by exposure, the cooling of the extremities caused by sympathetic vasoconstriction was not retarded by venous congestion, but frequently was accelerated (Fig. 3).

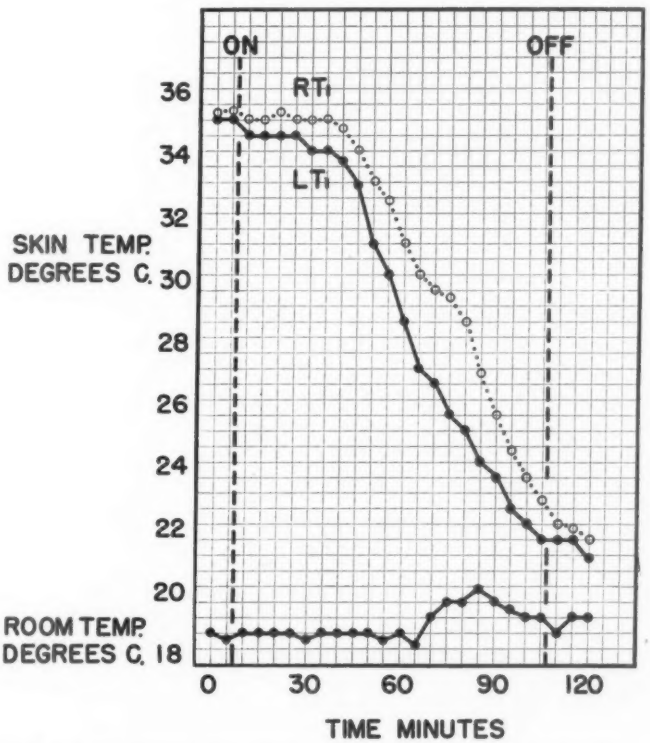


Fig. 3.—Effect of venous congestion upon cooling of the extremities caused by sympathetic nervous vasoconstriction. Chart of the temperature of the right great toe (RT_1), of the left great toe (LT_1), and of the room during an experiment on a normal subject. At the beginning of the experiment the subject was uncovered in the cool room. At 7 minutes (first vertical interrupted line) a cuff above the left knee was inflated to 50 mm. Hg. At 107 minutes the cuff was released.

Finally, observations were made upon the effects of venous congestion on the cooling of the extremities caused by raising them above the horizontal level.[10, 11] When both feet of a warmed, supine subject were raised 75 cm. above the bed, the toes became cooler. Congesting one leg by inflating a cuff above the knee to 50 mm. Hg did not prevent the

cooling of the foot on that side, but, on the contrary, apparently slightly enhanced the cooling caused by elevation (Fig. 4).

From these results it was concluded that blood flow in the skin of the extremities is not improved, and may be impeded, during venous congestion.

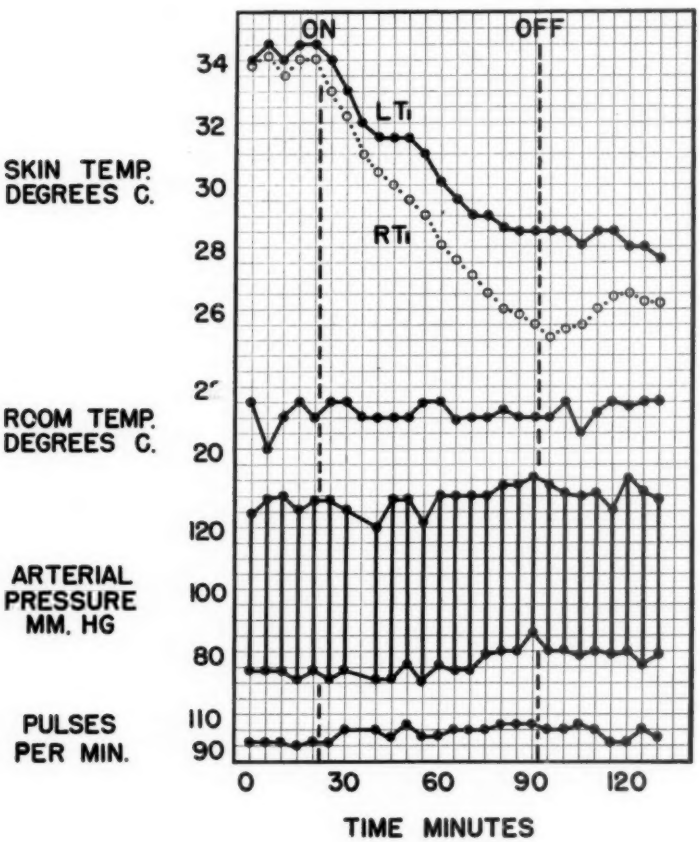


Fig. 4.—Effect of venous congestion upon cooling of the extremities caused by elevating the limbs. Chart of skin temperature of the left great toe (LT_1) and of the right great toe (RT_1); room temperature; arterial pressure; and pulse rate during an experiment on a normal subject. Throughout the experiment the subject was warmed by blankets and electric heating pads. At 22 minutes (first vertical interrupted line) both feet were raised 75 cm. above the bed, and a cuff above the right knee was inflated to 50 mm. Hg. At 92 minutes, the cuff was released.

PLETHYSMOGRAPHY

Evidence concerning the effect of venous congestion upon blood flow to the whole limb (skin and muscle) was obtained by examining the slope of the plethysmographic (Fig. 5) curves recorded during intermittent venous obstruction, i.e., plethysmographic blood flow curves.[9, 12] The slope of these curves was found usually to rise in a straight line at first, and then to level off with decreasing steepness into a plateau (Fig. 6, upper curve). Except after specific vasodilator procedures, a

slope of *increasing* steepness never occurred, as would have been expected had the rate of blood flow increased during the measurement. Venous pressure, as recorded by the Hamilton method[13] under similar conditions, always rose promptly upon inflation of the proximal cuff. Hence it was concluded that, as venous pressure rises after inflation of the cuff, blood flow does not increase, at least insofar as one can judge from the slope of the plethysmographic curves. Furthermore, it was shown that the plethysmographic curves were readily capable of indicating an increase in blood flow in the midst of a measurement. Such an increase in blood flow into a proximal part (forearm or calf) was produced artificially by allowing blood from the veins of the distal part (hand or foot) suddenly to escape into the proximal segment. Instead of keeping the cuff just distal to the plethysmograph (Fig. 5) at

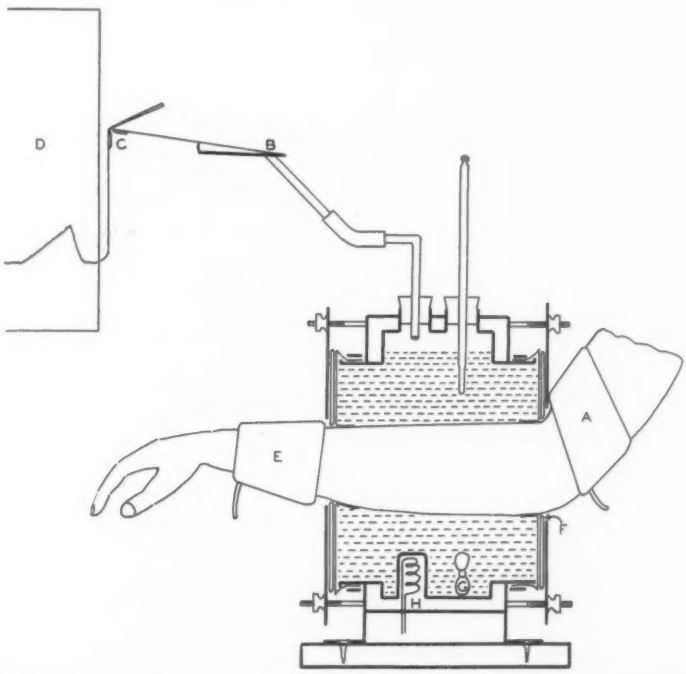


Fig. 5.—Diagram of a segment plethysmograph for the forearm or calf. *A* is the proximal pressure cuff; *B*, the Brodie's bellows, with special, hinged writing-lever, *C*; *D*, the recording drum; *E*, the distal pressure cuff; *F*, the supporting plates; *G*, the stirrer; and *H*, the heater.

greater than systolic pressure to exclude completely the circulation in the hand or foot,[14] the distal cuff was so regulated as to permit venous blood from the hand or foot to flow into the proximal segment in the midst of a plethysmographic blood flow measurement. The slope of the plethysmographic curve immediately indicated the additional inflow of blood by a sharp increase in steepness (Fig. 6, lower curve).

Further plethysmographic evidence was obtained by a technique

which allowed measurements of blood flow to be made in a part *during* venous congestion at any desired pressure. Again using the segment plethysmograph (Fig. 5), the distal cuff was first inflated to a pressure considerably less than diastolic, but greater than venous pressure. After a few seconds, as the venous pressure in the part of the extremity distal to this cuff approximated cuff pressure, equilibrium became established.

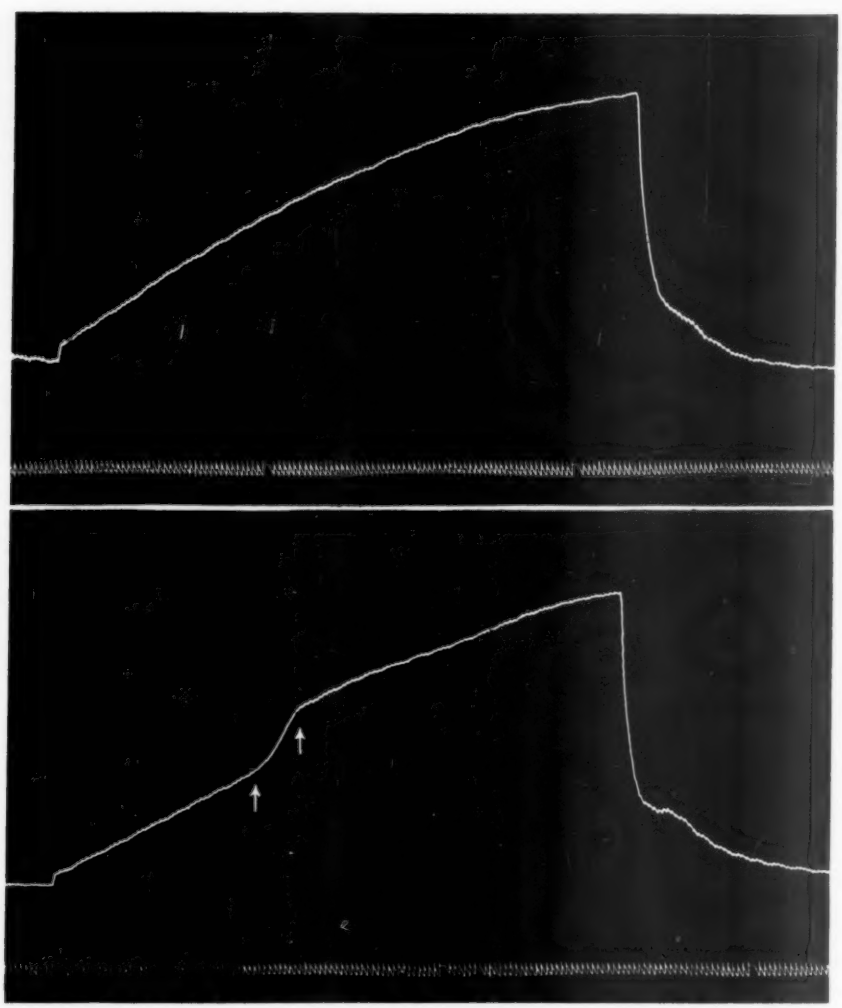


Fig. 6.—Plethysmographic tracings of blood flow to the forearm of a normal subject. The upper curve is of the routine type, obtained with the circulation to the hand occluded by a cuff at the wrist inflated to greater than systolic pressure. The lower curve shows the effect (between the arrows) of allowing blood from the veins of the hand to escape under the wrist cuff into the forearm segment.

This was shown in many experiments by using a second plethysmograph on this distal part to indicate the time at which no further change in volume was taking place. At that time the venous flow from the distal part must have been the same as the arterial flow into it. Moreover,

there was an important difference: the blood flow in the distal part was against a known congesting venous pressure (distal cuff pressure). The venous outflow from the distal part and the arterial inflow to the proximal part were then temporarily trapped within the proximal plethysmograph by intermittently inflating the proximal cuff at a pressure slightly less than that in the distal cuff. Thus, the blood flow both to the congested distal segment and to the proximal segment was measured simultaneously by one plethysmographic curve. As many measurements as desired of these combined flows were made. The pressure in the distal cuff was then raised to a higher pressure, but still less than diastolic, and, after equilibrium had become established, blood flow curves were again obtained from the plethysmograph on the proximal segment. These curves again indicated the sum of the blood flow directly into the proximal segment, and that into (out of) the distal part, which now, however, was congested at a higher venous pressure. Finally, the circulation in the distal part was completely excluded by a pressure in the distal cuff considerably greater than systolic. Blood flow curves then obtained from the proximal segment were considered accurate for that segment alone.[9, 14] Since the blood flow to such a proximal segment is known to be fairly constant,[9, 15] the consistent changes which were found in the previous combined flows obtained at different distal congesting pressures were attributed to the differences in the distal congesting pressures.

TABLE IV

EXCERPT FROM A PLETHYSMOGRAPHIC EXPERIMENT. COMBINED BLOOD FLOWS TO THE PROXIMAL (UNCONGESTED) AND DISTAL (CONGESTED) PARTS OF THE UPPER AND LOWER LIMBS OF A NORMAL SUBJECT

PULSE RATE BEATS/MIN.	ARTERIAL PRESSURE MM. HG	PRESSURE IN DISTAL CUFFS MM. HG	BLOOD FLOW C.C./MIN.	
			LEFT FOREARM	LEFT CALF
66	96/68	270*	21	37
66	100/66	30	111.5	78
66	96/68	60	69	70
68	98/68	30	118	86
68	98/68	60	51	59
66	100/68	30	92	69
68	98/68	60	57	58

*Circulation in hand and foot excluded.

The average of at least four measurements of blood flow at each level of pressure in the distal cuff was accepted as representative of the blood flow to the part or parts under the experimental conditions imposed (Table IV). Although there was some variation between individual measurements, there was no uniform tendency toward either an increase or a decrease in blood flow as any given pressure in the distal cuff was prolonged up to ten minutes. Allowance was made in the calculations for the blood flow to the small segment directly under the distal congesting cuff, by subtracting from the combined flows at the

lower congesting pressure an amount (5 c.c.) greater than the estimated flow in the part under the cuff without any pressure. This was done because, in other experiments, it was shown that local pressure on a limb, as from an inflated cuff, greatly reduces the blood flow in the part under pressure.

Twenty experiments were performed on nineteen different subjects, a few of whom had peripheral vascular disease. The subjects lay supine with their limbs at heart level, and were comfortably warmed by blankets and heating pads to produce generalized peripheral vasodilatation.[9] The pulse rate was counted from the plethysmographic tracings, and the arterial pressure was measured in a free limb by the usual auscultatory method.

TABLE V

EFFECT OF CHANGES IN DISTAL CUFF PRESSURE UPON COMBINED (PROXIMAL AND DISTAL) BLOOD FLOWS

CUFF PRESSURE		COMBINED BLOOD FLOW					
		INCREASED		NO CHANGE		DECREASED	
CHANGE	INSTANCES	INSTANCES	%	INSTANCES	%	INSTANCES	%
Increased	114	9	8	8	7	97	85
Decreased	84	67	80	9	11	8	9

As is shown in Table V, increasing the congesting pressure in the distal cuff reduced the combined flows in 85 per cent of the tests, whereas decreasing the congesting pressure increased the combined blood flows in 80 per cent of the experiments. Discrepancies in the results were only to be expected, for it has been shown that considerable spontaneous variations may occur in blood flow, especially to the distal parts of the limbs.[14]

DISCUSSION

In 1925, Lewis and Grant[16] reported that "when the arterial supply to a limb is occluded and released a state of vasodilatation is found," and that "a similar reaction occurs when venous pressure is increased." Further, they reported that "the reaction is not a response of the vessels to change of pressure within them, it is related to blood-flow debt"; and that, "the loss of vascular tone, which is responsible for the vasodilatation, occurs during the period of circulatory standstill or slowing."

As evidence for the latter statement a number of observations were reported, one of which was that, after ten to fifteen minutes of venous congestion at 40 to 50 mm. Hg, an increase was found in the amplitude of the pulsations recorded plethysmographically from the congested part.* This suggested to Lewis and Grant "that venous engorgement

*We have never observed an increase in the amplitude of the plethysmographic pulse waves during venous congestion similar to that illustrated in Lewis and Grant's article. This may be due to the fact that, during our experiments, greater precautions were taken to control the state of sympathetic nervous vasodilatation.[9] However, we do not doubt that a decrease in vascular tone does take place during the slowing of blood flow due to venous congestion, and that it might contribute to an increase in amplitude of the pulsations in the congested part.

causes dilatation of the vessels on the arterial side,'' although they gave no more direct evidence for this belief. It is important, however, to note that Lewis and Grant did not state, or intimate, that venous congestion in a limb is associated with an increase in blood flow over the resting (uncongested) level. On the contrary, they distinctly stated, as pointed out above, that the loss of vascular tone occurs during the period of circulatory *slowing,* and is related to blood flow *debt.* In other words, they believed that this reaction, like that to circulatory standstill from arterial occlusion, is a compensatory response to blood flow deprivation. Nevertheless, their work has been cited in support of the view that venous congestion in a limb may augment the arterial inflow to the limb.[1, 17]

It is unfortunate that the words ''reactive hyperemia'' have been used in connection with the loss of vascular tone that occurs during the period of circulatory arrest or slowing, for the term, strictly speaking, refers only to the increase in blood flow which follows the release of such an arrest or slowing. Obviously, ''loss of vascular tone'' and ''hyperemia'' (increase in blood flow) are not necessarily synonymous terms, particularly when there is a local obstruction in the circulation sufficient to retard the blood flow, even in vessels of low tone. A failure to appreciate this distinction of terms perhaps has contributed to the confusion that has arisen.

Hydrodynamically, it seems impossible that an increase in the flow of fluid through a collateral system of elastic tubes could occur when the egress of the fluid from the system is obstructed. This view has been substantiated in our laboratory by means of a mechanical schema constructed of various types of rubber tubes to represent arteries, arterioles, capillaries, and veins. With a constant head of perfusing pressure, any elevation of ''venous pressure,'' produced either by exerting pressure upon the large collapsible tubes representing the veins, or by raising the outflow level of these tubes, was accompanied by a decrease in flow through the schema.

Inasmuch as considerable criticism has been directed at the methods which apparently have revealed that an increase in blood flow occurs in vivo during venous congestion of a limb, we did not rely on a single method, but used four different types of measurements. The results show clearly and uniformly that blood flow does not increase in the limbs of human beings during rises of venous pressure produced by inflating blood pressure cuffs around them, but, on the contrary, usually decreases.

Concerning reactive hyperemia after the release of venous congestion in a limb, it undoubtedly occurs; however, it is quite small in amount and short in duration when compared with the reactive hyperemia which follows the release of arterial occlusion.[16] In the limbs of patients with severe obliterative arterial disease, the mechanism of reactive hyperemia is apparently being constantly invoked. This is shown by the fact that occlusion of the circulation is not followed, upon release, by any increase

in blood flow over the resting level.[18] It would seem that in such limbs there is always as much vasodilatation as is structurally possible under the stimulus of blood flow deprivation. These observations demonstrate the impossibility of improving the circulation in these limbs by reactive hyperemia, especially that which follows the release of venous congestion, which even in normal people is relatively slight.

Because of these considerations, we have not deemed it wise to use venous congestion over long periods of time in the treatment of patients with obliterative vascular disease. Hence, we have no observations upon its therapeutic effects in such cases. Furthermore, we did not wish to consider the variable ingrowth of collateral circulation in limbs after peripheral vascular accidents, because this would only have complicated the main problem we undertook to solve, namely, the effect of venous obstruction upon blood flow through a given vascular tree.

SUMMARY AND CONCLUSIONS

The blood flow in the extremities of human beings was measured with and without local venous congestion produced by inflating blood pressure cuffs on the proximal parts of the limbs. Four different methods were used: capillary microscopy, venous blood oxygen analysis, skin temperature measurements, and plethysmography. By all methods it was found that blood flow is not increased in the limbs during rises of venous pressure, but, on the contrary, is usually decreased.

REFERENCES

1. Linton, R. L., Morrison, P. J., Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion, AM. HEART J. **21**: 721, 1941.
2. Pritchard, W. H., Weisberger, A. S., Schroeder, E. F., Shipley, R. E., and Gregg, D. E.: The Acute Effects of Peripheral Venous Occlusion on Blood Flow in the Dog's Leg, Federation Proceedings **1**: 68, 1942.
3. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries, and Small Veins of the Human Skin, Am. J. Physiol. **29**: 335, 1911-1912.
4. Bordley, J., III, Grow, M. H., and Sherman, W. B.: Intermittent Blood Flow in the Capillaries of Human Skin, Bull. Johns Hopkins Hosp. **62**: 1, 1938.
5. Eichna, L. W., and Bordley, J., III: Capillary Blood Pressure in Man. Comparison of Direct and Indirect Methods of Measurement, J. Clin. Investigation **18**: 695, 1939.
6. Mulinos, M., and Shulman, I.: Vasoconstriction in the Hand From a Deep Inspiration, Am. J. Physiol. **125**: 310, 1939.
7. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. I, J. Biol. Chem. **61**: 523, 1924.
8. Holling, H. E.: Observations on the Oxygen Content of Venous Blood From the Arm Vein and on the Oxygen Consumption of Resting Human Muscle, Clin. Sc. **4**: 103, 1939.
9. Wilkins, R. W., and Eichna, L. W.: Blood Flow to the Forearm and Calf. I. Vasomotor Reactions: Role of the Sympathetic Nervous System, Bull. Johns Hopkins Hosp. **68**: 425, 1941.
10. Uprus, V., Gaylor, J. B., and Carmichael, E. A.: Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body. A Criticism of Methods, Clin. Sc. **2**: 301, 1936.
11. Roth, G. M., Williams, M. M. D., and Sheard, C.: Changes in the Skin Temperatures of the Extremities Produced by Changes in Posture, Am. J. Physiol. **124**: 161, 1938.

12. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, Heart **1**: 87, 1909-1910.
13. Hamilton, W. F., Brewer, G., and Brotman, I.: Pulse Pressure Contours in the Intact Animal. I. Analytical Description of a New High-Frequency Hypodermic Manometer With Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**: 427, 1934.
14. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb, Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, Clin. Sc. **3**: 119, 1938.
15. Abramson, D. I., and Ferris, E. B.: Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli, AM. HEART J. **19**: 541, 1940.
16. Lewis, T., and Grant, R.: Reactive Hyperemia in Man, Heart **12**: 73, 1925.
17. Collens, W. S., and Wilensky, N. D.: Intermittent Venous Occlusion in the Treatment of Peripheral Vascular Disease, J. A. M. A. **109**: 2125, 1937.
18. Landowne, M., and Katz, L. N.: Dynamics of Blood Flow in Thrombo-Angeitis Obliterans, J. Clin. Investigation **20**: 460, 1941.

DISCUSSION

DR. EDGAR V. ALLEN, Rochester, Minn.—It seems to me that Dr. Wilkins' paper is a very good illustration of how dependent the clinical practice of medicine is on such excellent studies in the laboratory. It also seems to me to represent a return to reason and to logic, because I am sure that it could never appeal to reason and logic to say that the arterial blood flow increased during a period of venous constriction. There is adequate evidence, I believe, to indicate the incorrectness of observations reported previously before this society that, using the thermostromuhr, one could demonstrate actual increase of arterial blood flow during venous compression.

It is only fair to point out that Dr. Wilkins has not said that repeated intermittent venous occlusion fails to increase the blood flow. He has said, however, and shown very conclusively, it seems to me, that, during the period of venous obstruction, there is no increase in the arterial blood flow.

Perhaps Dr. Wilkins has some evidence—I am sure he has—to indicate that which seems to be true also; that is, if one occludes the venous blood flow to the extremities intermittently, there is likewise no increase in the blood flow. I hope that he will comment on that.

DR. ROBERT R. LINTON, Boston.—I think I should say a word, inasmuch as I read the paper here two years ago.

The method of measuring blood flow with the thermostromuhr is, of course, a direct method. Whether it is an accurate method of measuring blood flow, I am not exactly sure, but I believe it indicates fairly accurately changes in blood flow, that is, whether it increases or decreases in volume. The data reported here today indicate blood flow only by inference.

Whether or not there is an increase or decrease with intermittent or complete venous occlusion of the main concomitant vein may still not be settled, but I think for clinical use venous occlusion is a very important adjunct in the treatment of peripheral arterial disease. In our experience it has been of little value in chronic obliterative arterial disease, but in acute arterial occlusion it is of inestimable value. I should like to cite a case of the latter.

A woman, 50 years of age, came in with a large carcinoma of the ovary, which I had to resect. In resecting it, I ligated her internal iliac artery. I did not realize at the time that I had damaged her external iliac artery, or I would have done a sympathectomy to improve the collateral circulation. Thinking I had not damaged her external iliac artery, I thought her leg would be all right. I saw her again an hour after the operation, at which time she was perfectly conscious. She said, "Doc, my foot is dead." And it was dead; you could stick pins into it. It was just as white as a sheet. No arterial pulsation or oscillations could be made out. The only thing I could think of for treatment was intermittent

venous occlusion. I applied a pressure cuff as high up on her thigh as possible. I inflated it to 50 mm. Hg. At the end of nine minutes there was a little color in the tips of her toes. We did not have a machine which would give a nine-minute period of occlusion, so for the next forty-eight hours I had the special nurses inflate the blood pressure cuff to 50 mm., leave it so for nine minutes, and then release it for one minute. At the end of that time we were able to decrease the "on" period so that we could use the machine.

In three weeks the patient was able to walk out of the hospital and is still walking on her leg, which is a perfectly good leg. It is not as good a leg as it was originally, but she can walk a mile without much difficulty, and the leg to outward appearances is perfectly normal. There are still no pulses palpable in it.

I just cite this case to impress upon you that intermittent venous occlusion, despite the laboratory evidence presented here today can be used to save extremities following acute major arterial occlusion to a limb.

DR. GEZA DE TAKATS, Chicago.—I agree with Dr. Linton that the clinical value of intermittent venous occlusion is very definite. I have no data to show whether or not the blood flow actually increases through the obstructed limb, but for some time we have maintained—and Dr. Linton has given experimental evidence of it—that there is a mechanical filling and stretching of the venous-capillary bed when the arterial flow is unobstructed and the venous flow is obstructed. I have always felt that that is the real cause of the clinical improvement we see; for the support of this contention we have published oscillometric curves, J. A. M. A. **108**: 1951, 1937.

DR. EDGAR V. ALLEN, Rochester, Minn.—It seems unwise to speak twice, but I cannot let pass without some comment what Dr. Linton has said relative to the use of intermittent venous occlusion for acute arterial occlusion. I am quite sure he did not want to imply, because of his experience in one case, that intermittent venous occlusion or venous occlusion of any type would save an extremity afflicted with sudden arterial occlusion.

Halsted showed many years ago that, if the iliac artery was ligated, there was complete recovery in almost all of the cases, even when no treatment was given. Gangrene ensued very rarely. These statements apply to ligation of the subclavian artery. It is true, therefore, that one may ligate the major arteries to the extremities with an extremely small incidence of gangrene.

Even in arterial embolism, in which the situation is substantially different because of the great arterial spasm which results from it, the incidence of spontaneous recovery is about 50 per cent without any treatment whatsoever.

So it would take more evidence, I believe, than one case or ten or more cases could furnish, to show that venous occlusion will save the extremity when its arterial circulation has been jeopardized by ligation of the chief artery.

DR. WILLIAM S. COLLENS, Brooklyn.—I should like to ask Dr. Wilkins whether he doubts the existence of the phenomenon of reactive hyperemia which follows the release of venous congestion. I saw no evidence of this phenomenon in his presentation.

Although Dr. Wilkins has demonstrated that venous congestion slows the circulation, one must be careful to interpret its clinical implications. I sometimes wonder whether laboratory evidence indicating the existence of a slowing of the circulation by venous congestion is necessarily a criterion with which to condemn intermittent venous occlusion as a therapeutic procedure.

When I ask that question I have in mind the work of Landis, with his evidence of an increase in capillary pressure that is associated with the state of venous congestion and an increase in capillary pressure after the release of venous congestion. I believe that these increases in capillary pressure produced by inter-

mittent venous occlusion in patients with arterial impairment favor the diffusion of nutrient substances from capillary to cell and aid in the healing of lesions. Obviously, this investigation does not tell the whole story.

As you know, Dr. Wilensky and I have for some years been proponents of intermittent venous occlusion therapy. As the years have gone by, we have continued to investigate the problem clinically. Since Dr. Linton has described to you one case, and Dr. Allen has criticized an experience with only one case, let me say that we have already had experiences in well over five hundred cases. When we try to remain unbiased and observe the patients during a control period without intermittent venous occlusion therapy, and then observe the sudden changes which are produced by the use of this therapy in patients with chronic obliterative disease, we become convinced very frequently that perhaps there is justification for intermittent venous occlusion therapy.

DR. ROBERT R. LINTON, Boston.—This [drawing on blackboard] is the aorta. This is the common iliac artery [indicating]. These are the external and internal iliac arteries [indicating].

I agree with Dr. Allen that Halsted's statements are perfectly true, i.e., if you tie the common iliac, the danger of gangrene in the extremity is not great in a young individual. One point that Dr. Halsted did not make, however, was that if you ligate the internal and the external iliac arteries, it is much more serious than if you ligate only the common iliac or the external iliac.

If you examine the vascular tree, you will see why that is true. If you tie the common iliac, the collateral circulation can get into the external iliac and down the leg through the internal iliac artery.

The reason I cited this case was merely to show that in an extreme case of vascular occlusion, when both the internal and external iliac arteries were occluded, the extremity was saved with intermittent venous occlusion when properly carried out. I have had other cases which proved the same thing, and I still feel that intermittent venous occlusion has a definite use in acute arterial occlusion.

DR. NATHAN D. WILENSKY, Brooklyn.—I should like to ask Dr. Wilkins whether he has employed his technique and made observations on patients with peripheral arterial disease with arterial impairment, using between 30 and 40 mm. of pressure and between one and two minutes of venous congestion.

DR. IRVING S. WRIGHT, New York.—I cannot let this discussion go by without saying that we conscientiously tried the use of this apparatus in twenty-eight cases over a period of one year, at the Post Graduate Hospital, and gave it up. This we would not have done if we had been convinced of its value.

DR. J. MURRAY STEELE, New York.—It seems to me that there are two quite distinct points in connection with this question. The paper under discussion was an attempt to answer the question whether or not, when one occludes the circulation with moderate pressure in a cuff, the circulation increases at the time the pressure is elevated. From another point of view, because this particular procedure has been used clinically, another question arises, namely, whether intermittent venous occlusion is good or bad for people with poor arterial supply. The two problems are quite distinct.

DR. NATHAN D. WILENSKY, Brooklyn.—The question whether improvement in circulation occurs with venous occlusion has still not been answered by these experiments. Although Sir Thomas Lewis demonstrated that a period of hyperemia follows the release of venous congestion, Wilkins does not present evidence that this phenomenon occurs. Yet we believe that the therapeutic rationale of venous occlusion lies in the production of reactive hyperemia.

Our therapeutic procedure did not allow for periods of congestion as long as ten minutes, for we found that the application of a congestive cuff to a limb

with an open lesion for this period of time could not be tolerated by the patient. We found it necessary to shorten the congestive period to about two minutes. In our original publication we reported on the use of two minutes of congestion and two minutes of release. We were convinced of the clinical value of this procedure and evidence of improved circulation by the relief of the patient's symptoms and the healing of ulcers.

DR. ROBERT W. WILKINS, Boston.—I am sorry that, despite our deliberate attempt to keep this presentation on a scientific basis, we seem to have entered the realm of feeling. I noticed how many times the words "I feel" and "I think" have been used. We really would prefer not to "feel" either way about it.

I should like to answer the questions in the reverse order from that in which they were asked, because that will keep the more recent discussions in our minds.

In regard to Dr. Collens' and Dr. Wilensky's objection to accepting laboratory evidence in therapeutic practice, it is a valid objection provided one doesn't call in any laboratory evidence, as, for example, Sir Thomas Lewis' or Landis' studies on reactive hyperemia. We are perfectly aware that reactive hyperemia occurs, and have published an extensive study on this subject. In Sir Thomas Lewis' original paper he used the term "reactive hyperemia" to indicate the reaction that occurs in a limb after deprivation of blood flow. It is a repayment, so to speak, not a thing which comes out of the blue; it occurs only after one first deprives the limb of its circulation.

I was most interested in Dr. Wilensky's comments as to the inability of a patient with acute obstruction of the circulation to tolerate long periods of venous obstruction, because I presume that he meant that it was clinically unpleasant or intolerable for the patient to undergo this procedure for a period of any duration. That, to me—if one wishes to accept only clinical evidence—would indicate that the blood flow, or, at least, the nourishment of the tissues during that period was impeded, and not enhanced.

We have used periods of venous obstruction of one or two minutes. We have also used longer periods. Dr. Linton, as you know, advocates the longer period. Dr. Collens and Dr. Wilensky advocate the shorter period. In our physiologic studies we have found no significant difference in the results, regardless of whether the pressure is used for longer or shorter periods of time.

We have used a pressure as low as 20 mm. Hg. We wish to emphasize, however, that these lower pressures produce little, if any, decrease in blood flow—in fact, little result whatever.

Returning to the matter of reactive hyperemia, if one wishes to produce reactive hyperemia in a limb, the best way to do it is to shut off the arterial inflow completely by a high cuff pressure. When you say "reactive hyperemia," as I pointed out a moment ago, you imply that the limb and its circulation are reacting to a period of blood flow deprivation. Katz and his associates have shown that a number of patients with obliterative vascular disease have, in a sense, a constant reactive hyperemia in their limbs, because, when one occludes the arterial circulation and then releases it, no reactive hyperemia, that is, no increase in blood flow over the resting level, occurs. Therefore, it would appear that these people have as rapid a blood flow as they can have, that the mechanism of reactive hyperemia is being constantly invoked, and that doing anything further with the hope of getting overpayment of the debt is of little value. In regard to the overpayment of the oxygen debt or of the blood flow debt by reactive hyperemia, most of the laboratory evidence would indicate that the debt is not overpaid. In fact, it is somewhat underpaid.

I have no comment on Dr. deTakats' question about the mechanical filling of the venous-capillary beds.

And that brings us to the final point, that Dr. Steele so nicely summed up for us, as to whether the results of this study can be brought to bear on the therapeutic value of intermittent venous occlusion in the treatment of peripheral vascular disease. Now, obviously, we did not wish to go beyond the conclusions of our experiments, but the implications are clear, and they have been taken by both those on the defense and those on the offense.

In response to Dr. Allen's question, we have not found that longer periods of intermittent venous occlusion are followed by an increase in resting blood flow after either one or many periods of occlusion. Naturally, we would have to carry on such experiments for days, and that brings in a very important point. We don't know whether there is a mechanical filling and emptying of the venous-capillary beds that is important. There may be. We did not want to consider whether ingrowth of collateral circulation would be promoted. Again, we have considered such an ingrowth to be a response to a deprivation of blood flow. Finally, we have no evidence on one very important point, namely, the lymphatic drainage from these limbs, which might conceivably be enhanced with the intermittent tension and relaxation of the limb as a whole, before and after venous obstruction.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

I. Effects on the Myocardial Cellular Structure*

William H. Dearing, M.D.,† Arlie R. Barnes, M.D.,† and Hiram E. Essex, Ph.D.‡
Rochester, Minn.

THESE studies were undertaken to ascertain (1) whether doses of digitalis, which were calculated to be equivalent to those administered clinically, produced demonstrable histologic changes in the mycardiums of experimental animals and (2) what is the minimal amount of digitalis (and its relation to the quantity of the drug used clinically) which will produce anatomic changes in the myocardiums of laboratory animals.

LITERATURE

Several investigators have reported that digitalis bodies are capable of producing organic changes in the myocardiums of animals. Levitski[1] administered galenical digitalis preparations and digitoxin in single and multiple doses to rabbits, dogs, and cats; he observed focal degenerative lesions in the myocardial fibers and evidence of inflammation in the connective tissue of the damaged hearts. Büchner[2, 3] described cellular changes in the hearts of the experimental animals on which Bauer and Fromherz[4] and Bauer[5] had studied certain cumulative phenomena produced by digitalis (digitoxin), gitalin, and strophanthin). The focal degenerative and exudative changes were essentially the same as those described by Levitski. Büchner pointed out that the lesions appeared three or more days after the digitalis had been administered, that they showed a predilection for the left ventricle, and that their origin was most likely related to a disturbance of the blood supply to the myocardium. He stated that these histopathologic changes are similar to those which occur in the myocardiums of patients who die shortly after an attack of angina pectoris[6] and to those in the hearts of rabbits after artificially induced anemia and strenuous exercise.[7, 8] Attention was called to the striking similarity between an attack of angina pectoris in man and the crying out and the motionless attitude assumed by cats after intravenous injections of digitalis. Weese and Dieckhoff[9] also reported cardiac lesions after the administration of toxic doses of digitoxin. The lesions were found in cats, but not in dogs and rabbits.

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

Received for publication July 19, 1942.

†Division of Medicine, Mayo Clinic.
‡Division of Experimental Medicine, Mayo Foundation.

Hu, Lieu, and Li[10] found anatomic lesions in the hearts of dogs (seventeen out of nineteen) which had received daily intravenous injections of digitoxin or lanadigin. Since these authors could not produce histopathologic changes in the myocardium of the frog, which does not have any coronary circulation comparable to that found in mammals, they concluded that digitalis bodies must bring about the myocardial lesions in the dog by constricting the coronary arteries. Lindner[11] observed histologic changes in the myocardium of the cat after the administration of digitoxin and oleandrin. He assumed that these lesions were primarily the result of metabolic changes in the myocardium and not of circulatory disturbances.

It is not clear from the work of the aforementioned investigators how the doses of digitalis bodies which produced anatomic changes in the myocardiums of experimental animals compared, on the basis of body weight, with those used clinically. The data to be presented in this paper throw some light on this question.

METHODS

Cats were used in these studies on the effects of digitalis on the cellular structure of the heart. Each animal was trained to lie quietly on its right side while electrocardiograms were taken. A control tracing was made each day until its contour remained fairly constant,[12] and until the animal was trained satisfactorily.

The animals were then weighed carefully, and the proper amount of digitalis was administered either by stomach tube or by intravenous or intramuscular injection. The dose of digitalis (or its glucosides) for each animal was calculated on the basis of percentage of the minimal lethal dose for the cat. Thirty per cent of the minimal lethal dose for the cat was assumed to be approximately equivalent to the therapeutic dose used in man. The cat unit served as a basis for the comparison of the dosage of digitalis for man and the cat. Eight different digitalis preparations were used: (1) digiglusin, ampule preparation of digitalis for parenteral administration; 1 c.c. was equivalent to 1 Hatcher-Brody cat unit; (2) digalen, ampule preparation of digitalis for parenteral administration; 2 c.c. were equivalent to 1 Hatcher-Brody cat unit; (3) digifoline, ampule preparation of digitalis for parenteral administration; 2 c.c. were equivalent to 1 Hatcher-Brody cat unit; (4) digifortis, tincture of digitalis for oral administration; 1 c.c. was equivalent to approximately 1¼ Hatcher-Brody cat units; (5) digitoxin, crystalline preparation; minimal lethal dose = 0.42 mg. per kilogram of cat (Hatcher-Brody method); (6) lanatoside A, crystalline preparation; minimal lethal dose = 0.35 mg. per kilogram of cat (Hatcher-Brody method); (7) lanatoside B, crystalline preparation; minimal lethal dose = 0.60 mg. per kilogram of cat (Hatcher-Brody method); and (8) lanatoside C, crystalline preparation; minimal lethal dose = 0.25 mg. per kilogram of cat (Hatcher-Brody method).

At various intervals after these drugs had been administered, observations were made on the behavior of the animals, frequent electrocardiograms were taken,[12] and finally those animals which did not die spontaneously were killed by placing them in a closed chamber and permitting them to breathe concentrated fumes of ether or chloroform. Necropsies were performed immediately. The brain and spinal cord were removed first.[13] Blocks of tissue from the heart were fixed in a 10 per cent solution of formalin after they had been removed from the following regions: (1) the anterior papillary muscle and the left ventricle wall, (2) the pos-

terior papillary muscle and the left ventricular wall, (3) the interventricular septum, (4) the right ventricular wall, (5) the right auricle or atrium, and (6) the left auricle or atrium. After proper fixation, these blocks of tissue were embedded in paraffin, sectioned, and stained routinely with hematoxylin and eosin. Some of the sections were stained with sudan III or Mallory's connective tissue stain. From each block of myocardium an average of six to twelve sections were made transversely (at right angles to the direction of the main muscle bundles), and a similar number of sections were made longitudinally (parallel to the direction of the main muscle bundles). An attempt was made to have the sections pass from the endocardial to the epicardial surfaces of the heart. An average of ninety-six sections were examined from each heart.

Blocks of tissue from the skeletal musculature (biceps, abdominal wall, and diaphragm), smooth musculature (stomach, duodenum, ileum, and uterus), kidney, and liver were fixed in a 10 per cent solution of formalin, sectioned, and stained. These tissues were examined routinely in each control animal and every animal which received digitalis.

The control animals were treated exactly like the experimental animals except that the controls did not receive digitalis. One control animal was killed for approximately every four experimental animals throughout the course of the studies.

RESULTS

A. Anatomic Studies of the Myocardiums of the Control Animals.—All of the cats which were used as controls were apparently in good health. The only abnormality found in the hearts of these animals was an occasional, fresh, subendocardial hemorrhage; it is possible that these hemorrhages were caused by the sudden death which was produced by ether or chloroform.

There were no macroscopic or microscopic evidences of any abnormality of the pericardium, the myocardium, or the coronary vessels in any of the control animals.

B. Anatomic Studies of the Myocardiums of Animals Which Had Received Therapeutic Doses of Digitalis.—Two types of experiments were designed to ascertain the effects of calculated therapeutic doses of digitalis on the anatomic structure of the heart. To one group of animals (Group A), the calculated therapeutic amount of the drug was administered in a single dose within a period of two to three minutes, or it was given in divided doses over a period of twenty-four to forty-eight hours; the myocardiums of these animals were examined microscopically from six to fifty-six days after the drug has been administered. To the other group of animals (Group B), the calculated therapeutic dose of digitalis was administered as in Group A, but, in addition, a daily estimated maintenance dose was given to the animals over a period of nineteen to sixty days. The maintenance dose was chosen arbitrarily on the basis of the body weight of the cat as compared with that of a man weighing 70 kg. For example, if 0.1 Gm. (1 cat unit) of digitalis whole leaf is the average daily maintenance dose for a man weighing 70 kg., a seventieth of 0.1 Gm. (or 0.00143 Gm.) was taken as the daily maintenance dose for each kilogram of cat. It is appreciated that this assumption is open to criticism (see consideration

of sources of error under "comment"). The hearts of the animals in Group B were examined histologically nineteen to sixty days after the administration of the digitalis bodies had been started.

TABLE I

ADMINISTRATION OF CALCULATED THERAPEUTIC DOSES OF DIGITALIS

GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Lanatoside A	20	Single dose, intravenous	14
Digalen	20	Single dose, intravenous	15
Digalen	30	Single dose, intravenous	6
Lanatoside C	30	Single dose, intravenous	11
Digitoxin	30	Single dose, intravenous	11
Lanatoside A	30	Single dose, intravenous	12
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12
Lanatoside A	30	Divided doses (48 hr.), intravenous	12
Digalen	30	Single dose, intravenous	14
Digitoxin	30	Single dose, intravenous	14
Lanatoside A	30	Single dose, intravenous	18
Lanatoside A	30	Single dose, intravenous	21
Digifortis	30	Single dose, oral	56

In Group A there were thirteen cats (Table I). No anatomic changes were observed in the hearts of any of the animals which had received a calculated therapeutic dose of digitalis. In the majority of the experiments the myocardium was examined within one to two weeks after the drug had been administered, for, as will be shown later, this is the time during which cellular changes are most likely to be found after the administration of a single toxic dose of digitalis.

In Group B there were eleven animals (Table II). The purpose of the experiments in this group was to ascertain whether, in digitalized animals which are receiving daily maintenance doses of the drug within the range of dosage used in man, demonstrable morphologic changes in the myocardium would develop. Five of the animals, which were first digitalized with a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose), received daily maintenance doses that were estimated to be the approximate equivalent in the cat of 1 cat unit daily for a man weighing 70 kg. The remaining six animals were also digitalized with 30 per cent of the minimal lethal dose of the drug, and then given daily the estimated equivalent of 2 cat units. The weight of a 70-kilogram man and the body weight of the cat were again used as the basis for the calculation of this daily dose.

In none of the animals in Group B did definite cellular changes in the myocardium develop, even when the digitalis was administered daily for periods as long as two months. All the animals tolerated the maintenance dose well except one cat which received digalen over a period

of forty days; in this case anorexia developed, and the animal lost weight during the last three weeks of administration of the drug.

TABLE II

DAILY ADMINISTRATION OF THE EQUIVALENT OF 1 OR 2 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE

GROUP B

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Digalen	1	Intravenous	19
Digifortis	1	Oral	19
Digifortis	1	Oral	30
Digalen	1	Intravenous	34
Lanatoside A	1	Intravenous	36
Digiglusin	2	Intravenous	20
Digifortis	2	Oral	30
Digalen	2	Intravenous	30
Lanatoside A	2	Intravenous	36
Digalen	2	Intravenous	40
Digifortis	2	Oral	60

C. Anatomic Studies of the Myocardiums of the Animals Which Had Received Toxic Doses of Digitalis. (a) Observations correlating dosage, duration of experiment, and histologic studies of the myocardium. It was difficult to group the animals in this series of experiments, for the number of animals was rather large and the manner in which the digitalis bodies were administered varied considerably. Perhaps it would simplify the presentation if one arranged the animals in this series into two major groups: (1) Group A_1, those animals which received a single toxic dose of digitalis and subsequently had the myocardiums examined microscopically after various periods of time; (2) Group B_1, those animals which received multiple doses of digitalis in various toxic amounts over different periods, and then had their hearts subjected to histologic study.

In order to ascertain approximately the smallest amount of digitalis, as well as the minimal time, necessary to produce these anatomic changes in the myocardium, a series of animals was given digitalis (or one of its glucosides) in single doses, varying from 20 per cent to 80 per cent of the minimal lethal dose. The animals were killed at various periods after the drug had been administered, and the myocardiums studied histologically.

Table III shows the amounts of the various single doses of digitalis bodies, the route of administration, the duration of the experiment after the drug was administered, and the results of the histologic examination of the myocardium. The data summarized in Table III indicate the following:

1. No demonstrable anatomic changes were observed in the myocardium after the administration of either 40 or 50 per cent of the minimal lethal dose.

2. Demonstrable histologic changes were observed in the hearts of two of eight cats which had received 60 per cent of the minimal lethal dose. One cat died before sufficient time had elapsed for myocardial changes to occur.

3. When the dose of the drug was raised to 70 or 80 per cent of the minimal lethal dose, the frequency of cellular changes in the heart increased.

4. Regardless of the size of the single dose of drug, no definite myocardial lesions were seen during the first four days.

5. When histologic changes occurred after the administration of single doses of digitalis, they were almost always present between the fifth and the twelfth day.

6. Cellular changes in the heart were produced by digitalis whole leaf or by crystalline products of digitalis (digitoxin, lanatosides A, B, and C).

7. In not all of the animals which received toxic doses of digitalis did myocardial lesions develop, even when the duration of the experiment was five days or more (that is, within the period during which lesions are producible).

Although it is interesting to know the minimal amount of digitalis which will produce myocardial damage when the drug is given in a single dose, it is more important from the standpoint of clinical application to ascertain the minimal amount which will cause myocardial injury when the drug is administered daily over a certain period of time, as in treating patients. With this thought in mind, a series of cats was digitalized with 30 per cent of the minimal lethal dose and then subjected to estimated daily doses of digitalis within the toxic range. These daily doses were estimated in the manner previously described in this paper.

As has been stated, the daily administration of the equivalent of 1 or 2 cat units to digitalized animals for a period as long as two months did not result in definite cellular changes in the myocardium. Table IV summarizes the effects of daily administration of the equivalent of 3, 4, 5.5, or 6 cat units on the myocardiums of the digitalized animals, and the data indicate the following:

1. In five of seven digitalized cats which received the equivalent of 3 cat units daily, lesions developed in the myocardium. Digitoxin, given intravenously, produced lesions after five days, and digifortis (tincture of digitalis), administered orally, induced myocardial damage within eleven days.

2. Histologic changes were found in all of the digitalized cats which received the daily equivalent of 4, 5.5, or 6 cat units over periods varying from seven to thirty days.

(b) Remarks on the age of the animal with respect to the production of myocardial lesions. It is important to point out that the factor of age significantly altered the results of this study. The old animals

TABLE III

RELATION BETWEEN THE HISTOLOGIC FINDINGS IN THE MYOCARDIUM AND THE ADMINISTRATION OF A SINGLE TOXIC DOSE OF DIGITALIS

GROUP A_1

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES IN MYOCARDIUM				
				PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
Digalen	40	Intravenous	12 days	No	No	No	No	No
Digiglusin	40	Intravenous	12 days	No	No	No	No	No
Lanatoside A	40	Intravenous	12 days	No	No	No	No	No
Lanatoside C	50	Intravenous	11 days	No	No	No	No	No
Digitoxin	50	Intravenous	13 days	No	No	No	No	No
Lanatoside A	50	Intravenous	14 days	No	No	No	No	No
Digalen	50	Intravenous	15 days	No	No	No	No	No
Digitoxin	60	Intravenous	12 hours	No	No	No	No	No
Lanatoside C	60	Intravenous	9 days	No	No	No	No	No
Lanatoside A	60	Intravenous	10 days	No	No	No	No	No
Digitoxin	60	Intravenous	10 days	Yes++++	Yes++++	Yes+++	Yes++	Yes++
Lanatoside C	60	Intravenous	11 days	Yes+++	Yes+++	Yes++	Yes+	Yes+
Digiglusin	60	Intravenous	12 days	No	No	No	No	No
Digalen	60	Intravenous	14 days	No	No	No	No	No
Digalen	60	Intravenous	15 days	No	No	No	No	No
Lanatoside A	60	Intravenous	15 days	No	No	No	No	No
Digitoxin	70	Intravenous	4 days	No	No	No	No	No
Lanatoside C	70	Intravenous	11 days	No	No	No	No	No
Digiglusin	70	Intravenous	12 days	Yes++	Yes++	Yes++	Yes+	Yes+
Digiglusin	75	Intravenous	3 days	No	No	No	No	No
Digiglusin	75	Intravenous	9 days	Yes++	Yes++	Yes+	No	No
Lanatoside A	75	Intravenous	12 days	Yes+++	Yes+++	Yes++	Yes±	Yes±
Digiglusin	80	Intravenous	39 minutes	No	No	No	No	No
Lanatoside A	80	Intravenous	3 hours	No	No	No	No	No
Lanatoside A	80	Intravenous	4 hours	No	No	No	No	No

Lanatoside A	80	Intravenous	6½ hours	No	No	No	No	No
Digalen	80	Intravenous	1 day	No	No	No	No	No
Lanatoside A	80	Intravenous	2 days	No	No	No	No	No
Lanatoside A	80	Intravenous	3 days	No	No	No	No	No
Digalen	80	Intravenous	4 days	No	No	No	No	No
Lanatoside A	80	Intravenous	5 days	Yes +	Yes +	No	No	No
Digitoxin	80	Intravenous	6 days	Yes +++	Yes +++	Yes ±	No	Yes +
Lanatoside A	80	Intravenous	7 days	Yes +	Yes +	No	No	No
Lanatoside A	80	Intravenous	8 days	Yes ++++	Yes ++++	Yes +++	Yes +	Yes +
Lanatoside C	80	Intravenous	9 days	No	No	No	No	No
Lanatoside A	80	Intravenous	10 days	No	No	No	No	No
Lanatoside A	80	Intravenous	10 days	Yes ++	Yes ++	Yes ++	No	No
Lanatoside C	80	Intravenous	11 days	No	No	No	No	No
Lanatoside A	80	Intravenous	12 days	Yes +++	Yes +++	Yes +	No	No
Digalen	80	Intravenous	12 days	Yes ++++	Yes ++++	No	No	No
Digiglusin	80	Intravenous	12 days	No	No	No	No	No
Lanatoside B	80	Intravenous	12 days	Yes +++	Yes +++	Yes +	No	No
Digitoxin	80	Intravenous	12 days	No	No	No	No	No
Tincture digitalis	80	Intravenous	12 days	Yes +++	Yes +++	Yes ++	Yes ++	Yes ++
Digifortis	80	Oral	13 days	Yes +	Yes ++	Yes +	No	No
Lanatoside A	80	Intravenous	14 days	Yes ++	Yes ++	No	No	No
Digalen	80	Intravenous	14 days	Yes +	Yes +	No	No	No
Lanatoside A	80	Intravenous	16 days	Yes +	Yes +	No	No	No
Digalen	80	Intravenous	17 days	Yes	–	–	–	–
Lanatoside A	80	Intravenous	21 days	No	No	No	No	No
Lanatoside A	80	Intravenous	23 days	Yes ++	Yes ++ healed	Yes ±	No	No
Digalen	80	Intravenous	24 days	Yes ++++	Yes ++++ healing	Yes +	No	No
Digalen	80	Intravenous	30 days	Yes +	Yes +	No	No	No
Lanatoside A	80	Intravenous	30 days	Yes ++	Yes ++ healed	No	No	No
Digalen	80	Intravenous	42 days	Yes ++	Yes ++ healed	No	No	No
Digalen	80	Intravenous	60 days	No	No	No	No	No

TABLE IV

RELATION BETWEEN THE HISTOLOGIC FINDINGS IN THE MYOCARDIUM AND THE DAILY ADMINISTRATION OF THE EQUIVALENT OF 3, 4, 5.5, OR 6 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE

GROUP B_1

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES IN MYOCARDIUM				
				PAPILLARY MUSCLE AND LEFT VENTRICLE	INTER-VENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
Digitoxin	3	Intravenous	5	Yes++++	Yes++++	Yes+++	Yes+++	Yes+++
Digifortis	3	Oral	11	Yes++++	Yes++++	Yes++	Yes+	Yes+
Tincture digitalis	3	Intravenous	13	Yes++++	Yes++++	Yes++	Yes+	Yes+
Tincture digitalis	3	Intravenous	14	No	No	No	No	No
Tincture digitalis	3	Intravenous	18	No	No	No	No	No
Lanatoside A	3	Intravenous	25	Yes+++	Yes++	Yes±	No	No
Lanatoside A	3	Intravenous	30	Yes±	Yes±	No	No	No
Digiglusin	4	Intravenous	7	Yes++	Yes++	Yes±	No	No
Digifortis	4	Oral	14	Yes++	Yes++	No	No	No
Digifortis	4	Oral	19	Yes+±	Yes+	Yes+	No	No
Digifortis	4	Oral	30	Yes+	Yes+	Yes±	No	No
Lanatoside A	5.5	Intravenous	30	Yes++++	Yes++++	Yes++	Yes+	Yes+
Digifortis	6	Oral	30	Yes+	Yes±	No	No	No

tolerated the digitalis bodies less well than the young ones, that is, the old animals were more prone to die after single or multiple doses of digitalis had been administered and more likely to show lesions in the myocardium, and these myocardial lesions were more likely to be extensive. For example, a young cat which received the daily equivalent of 6 cat units of digifortis (tincture of digitalis) for thirty days showed far less extensive lesions in the myocardium than did an old cat which received the daily equivalent of only 3 cat units of digifortis for eleven days.

(c) The myocardial histologic changes produced by toxic doses of digitalis. So far we have mentioned only the dosage of digitalis and the intervals in relation to the myocardial lesions. Let us now discuss the sequence of pathologic events in the development of these myocardial lesions. It must be kept in mind that the histologic changes were found only after administration of toxic doses of digitalis, and not after the administration of calculated therapeutic doses of this drug.

Among the early microscopic changes which were seen in the hearts of animals that had died spontaneously or had been killed within one to four days after single or multiple toxic doses of digitalis bodies were zones of capillary engorgement and regions of muscle which stained deeply with eosin and exhibited a more or less homogeneous appearance and coarse granulations in the perinuclear cytoplasm, or rather large clear spaces around the nuclei of the muscle fibers. None of these were considered sufficiently definite to justify classifying them as evidence of clear-cut histologic changes. When they occurred they were not counted in our results as myocardial lesions. This position was taken to minimize the inclusion of falsely positive observations.

Our anatomic studies confirm those of Levitski and Büchner. The earliest definite cellular change was a degeneration of the myocardial fibers. The latter seemed to vacuolate, fragment, and disintegrate in focalized zones of the myocardium (Fig. 1). Hemorrhage was often seen in the regions of degeneration of muscular fibers (Fig. 2). Later, exudative cells entered the region of degeneration (Fig. 3). These exudative cells included neutrophilic leucocytes, lymphocytes, and histiocytes. At this stage the lesions were typical of inflammation. As the degenerative and exudative components began to subside, the connective tissue cells (fibroblasts) proliferated (Fig. 4). If the administration of digitalis was discontinued and the dosage of the drug had not been too large these myocardial lesions began to heal. The degenerating material and the exudative cells were replaced gradually by fibroblasts. The recently healed lesions were composed of loosely interwoven fibroblasts (Fig. 5). These focalized scars were scattered throughout the myocardium. After a time these regions of scar tissue contracted, and it was sometimes difficult to locate them in the heart after six to eight weeks (unless the damage to the myocardium had been extensive).

As previous workers have pointed out, there was a predilection of these focalized lesions for certain regions of the myocardium. The

Fig. 1.—Early degeneration of the myocardial fibers after administration of a toxic dose of digitalis (×450).

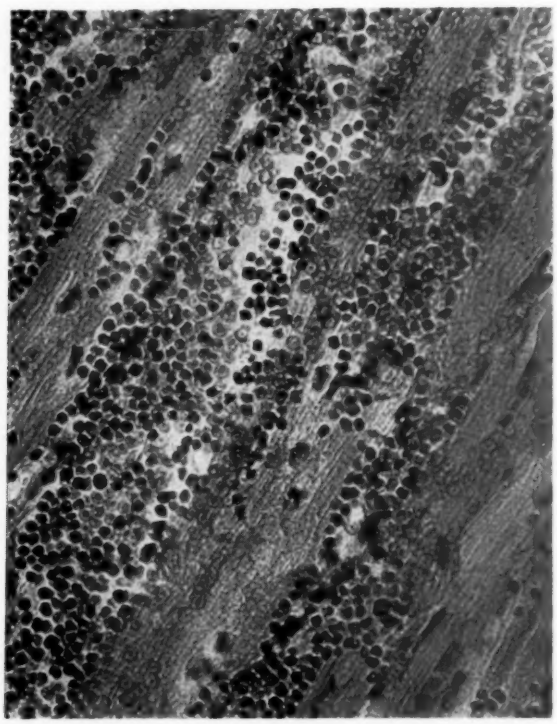


Fig. 2.—Hemorrhage into zones of degenerating myocardium after administration of a toxic dose of digitalis (×450).

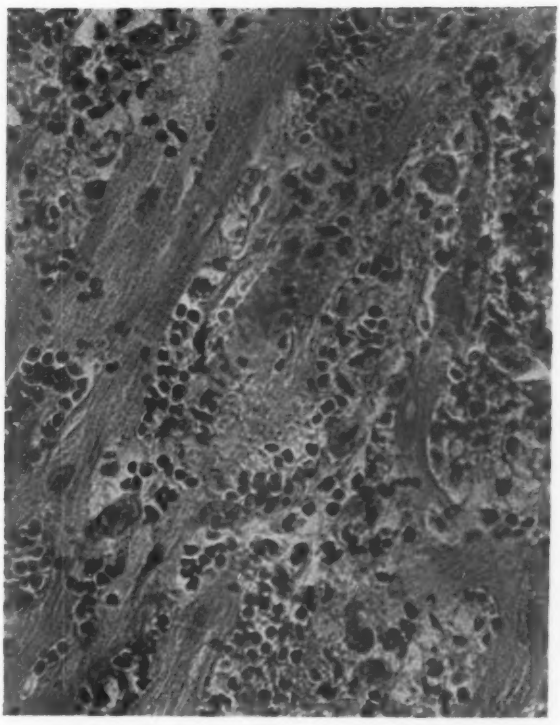


Fig. 3.—Degeneration of the myocardial fibers, plus numerous exudative cells after administration of a toxic dose of digitalis (×450).

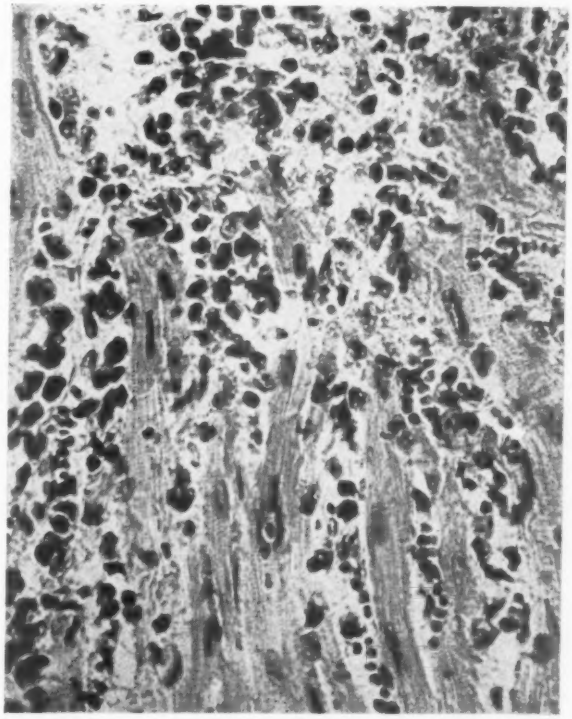


Fig. 4.—Early signs of healing in myocardial lesion after administration of a toxic dose of digitalis. Fibroblasts are proliferating (×450).

anatomic changes were more likely to be found in the papillary muscle than anywhere else in the heart; next in frequency were the left ventricular wall and the interventricular septum. Histologic changes were observed in the right ventricular wall, but they were much less frequent and extensive than those in the left ventricular wall. Demonstrable cellular changes in the auricles and atria were seen in only a few animals.

There was perhaps a tendency for the histologic changes to be more frequent and more extensive in the subendocardial region of the myocardium than in other regions, but they were also often found throughout the entire depth of the ventricular wall, from the epicardium to the endocardium.

Fig. 5.—Recently healed myocardial lesion produced by digitalis. Fibroblasts have replaced the destroyed myocardial fibers (×450).

Before concluding our remarks on the histologic studies of the heart, it might be well to emphasize again that no evidence of any abnormality of the coronary arteries, including arteriosclerosis, was observed in any of the controls or the animals treated with digitalis.

D. Anatomic Studies of the Skeletal and Smooth Musculature of the Control Animals and of Those Treated With Digitalis.—One might ask whether toxic doses of digitalis which were capable of producing lesions in the cardiac muscle were able also to cause cellular changes

in the skeletal or smooth musculature of the experimental animals. Histologic study of the skeletal musculature (biceps, abdominal wall, and diaphragm) and the smooth musculature (stomach, duodenum, ileum, and uterus) in each of the control animals and in the animals which had received therapeutic or toxic doses of digitalis bodies failed to reveal any evidence of pathologic changes. These studies of the extracardiac musculature were made routinely on every animal used in these experiments.

E. Observations on Signs of Intoxication in the Cats Treated With Digitalis.—Vomiting for a few hours and anorexia for one day or so were observed in some of the animals which received calculated therapeutic doses of digitalis. No significant arrhythmias were noted after calculated therapeutic doses of digitalis. The cardiac rate in these animals was slowed, accelerated, or unchanged. In our experiments the cardiac rate was found not to be a reliable guide to the quantity of digitalis administered. A few days after a therapeutic dose of digitalis the appearance of the animals was not different from what it had been in the control period before digitalization.

The incidence of vomiting and anorexia was greater in the animals which received toxic doses of digitalis than in those which received therapeutic doses. Not all the animals vomited, even after 80 per cent of the minimal lethal dose had been administered. Loss of weight occurred in the severely intoxicated cats, and drowsiness was noted fairly frequently in these animals.[13] Arrhythmias of various types occurred with toxic doses of the drug.[12] Many of the animals which were intoxicated with digitalis showed an accelerated heart rate instead of bradycardia. The latter, however, was observed commonly. Only a few of the animals exhibited the so-called anginal syndrome, as described by Büchner,[3] after an intravenous injection of digitalis. These signs disappeared after a brief period.

Some of the animals which had been quite ill and had shown suggestive signs of myocardial injury in their electrocardiograms recovered completely. Their appetites returned to normal, they gained weight, the electrocardiograms resumed contours similar to those of the control periods, and, to all intents and purposes, the animals were normal. These animals had had myocardial lesions which healed.

F. Preliminary Observations on the Relation Between Dosage of Digitalis and Myocardial Lesions in Hyperthyroid Cats.—Hyperthyroidism was induced with thyroid extract or thyroxin in a series of cats. Extensive myocardial lesions were observed in some of the hyperthyroid animals which had received a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose). As has been shown, this dose of digitalis did not produce any demonstrable anatomic changes in the normal animal. Toxic doses of digitalis either killed the hyperthyroid animals promptly or caused extensive myocardial damage. These experimental results will be reported in a separate paper.

COMMENT

Discussion of Sources of Error in Our Experiments on Digitalis.—The bio-assay of the potency of digitalis leaves introduced an unavoidable source of error into our experiments. It is agreed by everyone that the bio-assay of digitalis is not entirely satisfactory; yet it is perhaps the most reliable method available at the present time. It was necessary for us to rely on bio-assay in order to ascertain the potency of our digitalis leaves, even though it was apparent to us that 0.1 Gm. of a given standardized preparation of digitalis leaves may be lethal for one cat which weighs 1 kg. and not for another cat of the same weight under identical experimental conditions. There is no known simple method of controlling the biologic variables which contribute to the production of differences of sensitivity to drugs among various individuals of the same species. Even when crystalline products of digitalis, which can be standardized gravimetrically, are used, the minimal lethal dose for the cat may vary considerably as a result of variations of individual sensitivity to the drug. Therefore, the size of the dose of any given preparation of digitalis which is required to produce a certain response in the cat is only an approximate value.

In our present state of knowledge, one is forced to use animals to assay the digitalis which is to be used in the treatment of patients. There is no assurance that man and animal are equally sensitive to digitalis. It is thought, however, that the sensitivity to digitalis of the cat is more like that of man than is the sensitivity of any other commonly used laboratory animal. Although experimentation in the future may indicate that the cat unit is not an adequate guide for the estimation of the dosage of digitalis in man, we have used this unit in our experiments to compare the dosage of digitalis in man and in the cat.

For the lack of a better method, we have assumed arbitrarily that, if a daily dose of 0.1 Gm. of a given preparation of digitalis is necessary to maintain digitalization in the case of a 70-kilogram man, a seventieth of 0.1 Gm., or 0.00143 Gm., will maintain digitalization in a cat which weighs 1 kg. This assumption is obviously open to criticism, but we are not aware of a better and simpler method of ascertaining for the cat the dose of digitalis which corresponds to 1 cat unit in man.

It should be kept in mind that these experiments on digitalis were done, to the best of our knowledge, on healthy cats that had normal myocardial structure and normal vascular systems. Myocardial and arterial diseases were not complicated factors in our animals.

It might be well to point out that our method of histologic study does not give information regarding the multitude of chemical and other changes which may occur in the myocardium before demonstrable morphologic changes are observable. The absence of myocardial lesions soon after the administration of toxic doses of digitalis does not mean that chemical changes in the myocardium, which may lead later to cellular necrosis, have not already occurred.

SUMMARY

No microscopic pathologic changes were found in the myocardiums or coronary arteries of the control animals.

No evidence of histologic changes was found in the myocardiums of the experimental animals after the administration of calculated therapeutic amounts of digitalis (30 per cent of minimal lethal dose) in single or divided doses, given over a period of forty-eight hours. The histologic studies were made after a minimum of six days and a maximum of fifty-six days.

Myocardial lesions were not produced in our experimental animals when they were digitalized rapidly with a calculated therapeutic dose of digitalis, and were then given daily maintenance doses of the drug which were estimated to correspond to either 1 or 2 cat units for a man weighing 70 kg. The histologic studies were made after a minimum of nineteen days and a maximum of sixty days.

In our experiments, 60 per cent of the minimal lethal dose was the smallest amount of digitalis which, when given as a single dose, produced definite evidence of myocardial lesions. This dose of digitalis is in the toxic range.

The frequency with which myocardial lesions occurred increased as the size of the single dose of digitalis was increased to 80 per cent of the minimal lethal dose.

Myocardial lesions were not found until five or more days after the single toxic doses of digitalis had been administered.

Histologic changes were not observed in the hearts of all the animals which had received toxic amounts of digitalis, even when the quantity of the drug was 80 per cent of the minimal lethal dose.

Histologic changes were produced in the myocardium when the animals were digitalized rapidly with a calculated therapeutic dose of digitalis, and were then given daily quantities of the drug which were estimated to correspond to 3, 4, 5.5, or 6 cat units for a man weighing 70 kg. The equivalent of 3 cat units daily of parenterally administered digitoxin caused myocardial lesions within five days in one animal, whereas the same amount of orally administered tincture of digitalis produced myocardial lesions within eleven days in another animal. The digitalized animals in this group which received daily doses of digitalis in the toxic range had their myocardiums examined microscopically after a minimum of five days and a maximum of thirty days.

Histologic changes in the heart were produced by digitalis whole leaf or by crystalline products of digitalis (digitoxin, lanatoside A, lanatoside B, and lanatoside C).

The sequence of pathologic changes in the myocardium after the administration of toxic doses of digitalis was studied. The observations of Levitski[1] and Büchner[3] were confirmed.

The myocardial lesions were focal in distribution, and were more frequent in the papillary muscles and in the left ventricular wall than

in other regions. This also confirmed the observations of Levitski and Büchner.

Animals which survived the toxic doses of digitalis recovered completely in three or more weeks. Animals which had myocardial scars produced by digitalis (healed lesions) appeared entirely normal after three to four or more weeks.

Myocardial lesions were more prone to develop in old animals after the administration of digitalis than in young ones. This difference in sensitivity to the drug was not related to arteriosclerosis, for no evidence of this disease was found in the cardiac arteries or arterioles of any of the cats.

Experimental hyperthyroidism increased the sensitivity of the animals to digitalis. Myocardial lesions were found after the administration of calculated therapeutic doses of digitalis to hyperthyroid cats.

No evidence of anatomic changes was seen in the skeletal musculature or the smooth musculature of any of the animals which had received digitalis in therapeutic or toxic quantities.

REFERENCES

1. Levitski, A. I.: O patologohistologicheskikh izmïeneniyakh serdtsa pri ortravleniyakh zhivotnikh (krolikov, sobak i koshek) preparatami naperstyanki; (k etiologii eksperimentalnavo miokardita). [Pathologohistological changes of the heart if animals (rabbits, dogs and cats) are poisoned with digitalis preparations; (on the etiology of experimental myocarditis)], S.-Petersburg, 1904, V. P. Meshtsherski.
2. Büchner, Franz: Herzmuskelnekrosen durch Digitalisglykoside, Klin. Wchnschr. **33**: 1237, 1933.
3. Büchner, Franz: Herzmuskelnekrosen durch hohe Dosen von Digitalisglykosiden, Arch. f. exper. Path. u. Pharmakol. **176**: 59, 1934.
4. Bauer, H., and Fromherz, K.: Ueber die Kumulierung der Digitalisglykoside, Klin. Wchnschr. **12**: 973, 1933.
5. Bauer, Hellmut: Zur Kenntnis der Ursachen der Kumulierungserscheinungen der Digitalisglykoside; Ergebnisse physiologischer Methoden, Arch. f. exper. Path. u. Pharmakol. **172**: 699, 1933.
6. Büchner, Franz: Die Rolle des Herzmuskels bei der Angina pectoris, Beitr. z. path. Anat. u. z. allg. Path. **89**: 644, 1932.
7. Büchner, Franz: Das morphologische Substrat der Angina pectoris im Tierexperiment, Beitr. z. path. Anat. u. z. allg. Path. **92**: 311, 1933.
8. Büchner, Franz, and von Lucadou, W.: Elektrokardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimenteller Coronarinsuffizienz, Beitr. z. path. Anat. u. z. allg. Path. **93**: 169, 1934.
9. Weese, H., and Dieckhoff, J.: Zur Kumulation der Digitalisglykoside, Arch. f. exper. Path. u. Pharmakol. **176**: 274, 1934.
10. Hu, C. H., Lieu, V. T., and Li, R. C.: Anatomical Changes in the Hearts of Dogs and Frogs Poisoned by Glucosides of the Digitalis Group, Chinese M. J. supp. 1, 31, 1936.
11. Lindner, Werner: Untersuchungen zur Kumulation der Digitaliskörper, Arch. f. exper. Path. u. Pharmakol. **192**: 155, 1939.
12. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. II. Effects on the Electrocardiogram, AM. HEART J. **25**: 666, 1943.
13. Dearing, W. H., Barnes, A. R., Kernohan, J. W., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. IV. Effects on the Cellular Structure of the Central Nervous System, AM. HEART J. In press.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

II. Effects on the Electrocardiogram*

William H. Dearing, M.D.,† Arlie R. Barnes, M.D.† and
Hiram E. Essex, Ph.D.‡
Rochester, Minn.

THE purpose of this investigation was to ascertain whether characteristic electrocardiographic patterns accompany the myocardial lesions produced by digitalis, as described in a previous paper.[1]

LITERATURE

Numerous investigators have described the effects of digitalis bodies on the electrocardiogram of man and animals. Nicolai and Simons[2] administered 3 Gm. of powdered digitalis leaves daily for five days to four human subjects and observed an increase in the amplitude of the T wave. Straub[3] gave toxic doses of strophanthin (3 mg.) to anesthetized cats; he observed inversion or elevation of the T wave. Selenin[4] observed in morphinized dogs an increase in the size of the T wave after the administration of digitoxin. Bickel and Tsividis[5] injected digitalysatum into rabbits and observed a slight decrease in the height of the T wave with moderate doses (1 c.c. per kilogram) and a decrease in height of the T wave with larger doses. Bickel and Pawlow[6] came to a similar conclusion after administering small and large doses of strophanthin and digistrophan to dogs and rabbits. Rothberger and Winterberg[7] did not observe any change in the electrocardiogram of the dog with small doses of strophanthin; large doses sometimes produced inversion of the T wave. Cohn, Fraser, and Jamieson[8] concluded that digitalis (average of 0.4 Gm. daily) produced a lowering of the T wave, and later an inversion. They stated that the changes in the T wave developed as early as thirty-six to forty-eight hours and persisted as long as twenty-two days after the digitalis had been administered. White and Sattler[9] considered a decrease in the amplitude of the T wave to be the earliest sign of the action of digitalis. They gave 2 to 3 Gm. of standardized digitalis over periods of seven to fourteen days to human subjects.

Robinson and Wilson[10] reported negative T waves in cats which had received 10 per cent of the calculated minimal lethal dose of digitalis every ten minutes. The negative T wave appeared when approximately

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

Received for publication July 19, 1942.

†Division of Medicine, Mayo Clinic.
‡Division of Experimental Medicine, Mayo Foundation.

25 per cent of the minimal lethal dose had been administered. Harris and Edin[11] described a depression of the RS-T segment in the electrocardiograms of human subjects after the administration of 1 dram (3.7 c.c.) of digitalis a day for a fortnight. The depressed RS-T segment was regarded as a sign of digitalis intoxication. Pardee[12] reported electrocardiographic changes in man after giving 1 minim (0.06 c.c.) of standardized tincture of digitalis per pound (0.5 kg.) of body weight. The T wave in Lead III was first decreased in height and then inverted; these changes appeared two to four hours after the digitalis had been administered, reached a maximum in six to seven hours, and persisted for a period of twenty-four hours without change. Pardee[13] tested forty-one persons with four different standardized tinctures of digitalis and concluded that the changes in the T wave could be used as a measure of the minimal effective dose. McCulloch and Rupe[14] studied the effects of digitalis on the electrocardiograms of children. They stated that, with full digitalization, the changes were not constant in all cases. Marvin, Pastor, and Carmichael[15] administered 1.5 Gm. of standardized digitalis per 10 pounds (4.5 kg.) of body weight and observed reversal of the T waves or depression of the RS-T segment in twenty-nine of thirty subjects.

DeGraff and Wible[16] observed in cats an elevation of the RS-T segments after the administration of digitalis. They pointed out its similarity to the RS-T change which occurs soon after myocardial infarction. Yacoel and Papapanayotou[17] reported that an increase in the height of the T waves accompanied improvement in the condition of patients who were receiving digitalis and ouabain. This is in contrast to the observations of Pardee. Cohn and Stewart[18] observed changes in the direction of the T wave in dogs after the administration of therapeutic doses of digifoline (0.5 c.c. per kilogram). Kahlson[19] observed an increase in the height of T waves in cases of heart disease and a decrease in their height in normal persons after the administration of digitalis. Brams[20] studied the effects on dogs and cats of various preparations of digitalis in therapeutic and toxic doses. Constant lowering of the T wave did not occur and in no case was a negative T wave observed. He doubted that changes in the T wave could be used as a criterion of the action of digitalis, as Pardee had suggested. The same conclusion was reached by Brams and Gaberman[21] when they administered an average of 4.5 c.c. of digifoline to human subjects until nausea, vomiting, precordial distress, or heart block occurred. Schwartz and Weiss,[22] Blumenfeldt and Strauss,[23] and Grünbaum[24] came to similar conclusions about the T wave after the administration of digitalis to human subjects. On the contrary, Bromer and Blumgart[25] regarded the T-wave changes as a quantitative index of the amount of digitalis in the body.

Larsen, Neukirch, and Nielsen[26] studied the effects of therapeutic doses of digitalis on fifteen young adults; in fourteen of these subjects

the T wave became lower in one or more leads. Herles[27] pointed out that changes in the RS-T segment and T wave occurred primarily in Leads I and II with left ventricular strain, and predominantly in Leads II and III with right ventricular strain. Winternitz[28] called attention to two types of changes in the RS-T segment after the administration of digitalis, namely a trough-shaped or bowl-shaped depression, and an oblique depression.

The foregoing review indicates the diversity of opinion regarding the nature of the electrocardiographic changes, and also regarding the interpretation of their significance, after the administration of any given dose of digitalis.

Several workers have published papers dealing with the problem in which we are primarily interested, namely, the relation between electrocardiographic changes and the myocardial damage produced by toxic doses of digitalis bodies. Bauer[29] studied the electrocardiograms on some of his cats. He intimated that the negative T wave was an indication of cardiac damage. Korth and Spang[30] observed depression or elevation of the RS-T segment in cats after the administration of toxic amounts of digitoxin in single or multiple doses; depression of the RS-T segment was not associated with myocardial necrosis, but elevation of the segment did constitute evidence of necrosis in the cardiac muscle. Spang and Korth[31] amplified their previous studies to emphasize their observation that depression of the RS-T segment does not indicate the presence of myocardial lesions. Baur and Reindell[32] studied the tracings from cats which received digitoxin in small and in large doses (0.025 to 0.1 mg. per kilogram). They described ten different electrocardiographic changes, and stated that the patterns after the administration of small doses of digitalis (unassociated with cardiac lesions) may be the same as those after the administration of large doses (associated with myocardial necrosis). It is not quite clear which patterns were indicative of myocardial damage.

METHODS

With a few exceptions, the electrocardiographic studies with digitalis were made on the same cats which were used in the previously described experiments[1] dealing with anatomic changes in the myocardium.

A Sanborn portable cardiette served to record the electrocardiograms. The machine was standardized carefully at the beginning of each lead. A deflection of 1 cm. represented a potential difference of 1 millivolt. The three conventional leads were used in all experiments (Lead I, right foreleg and left foreleg; Lead II, right foreleg and left hindleg; Lead III, left foreleg and left hindleg).

Small areas were shaved on the proper extremities for the attachment of the lead wires. A commercial electrode paste was used to insure good contact between the electrodes and the skin of the animal. As a further precaution, gauze was placed between the two forelegs and between the two hindlegs to prevent contact of the extremities while the electrocardiograms were being made.

Each animal was trained to lie quietly on its right side on a table over which a rubberized cushion had been placed. During this period of training, electro-

cardiograms were made daily. When the animal was trained satisfactorily and the electrocardiograms had attained a fairly constant contour (which persisted for several days), digitalis was administered.

It is not necessary to repeat the names of the various preparations of digitalis, their dosage, methods of administration, and so forth, for they were the same as described in the paper[1] dealing with the anatomic studies on the myocardium.

RESULTS

It is planned to attempt to correlate the dosage of digitalis, the electrocardiographic changes, and the anatomic studies on the myocardium.

A. Electrocardiographic Studies of the Control Animals.—There was considerable variation of cardiac rate. Sinus arrhythmia was observed frequently. The T wave in Lead III was often negative. A slight elevation of the RS-T segment was seen in some of the control animals and in some of the experimental animals during the control period (before administration of digitalis).

The histologic studies of the myocardium of the control animals failed to reveal any evidence of structural disease.

B. Electrocardiographic Studies of Animals Which Received Therapeutic Doses of Digitalis.—In order to simplify the presentation of the studies correlating the electrocardiographic changes with the dosage of digitalis and the histologic investigations of the myocardium, the experimental animals were divided into two groups: (1) Group A, those which received the calculated therapeutic amount of digitalis (20 or 30 per cent of the minimal lethal dose) in a single dose within an interval of two to three minutes, or in divided doses over a period of forty-eight hours; (2) Group B, those which received the calculated therapeutic amount of digitalis in a single digitalizing dose, and, thereafter, daily maintenance quantities of the drug over a period of nineteen to sixty days. The daily maintenance doses were calculated as indicated in a previous paper;[1] they were the estimated equivalent of either 1 or 2 cat units per day (a 70-kilogram man and the body weight of each cat were used as the basis for these calculations).

In both Group A and Group B, electrocardiograms were taken, as a rule, six hours after the drug had been administered, and then once or twice daily throughout the duration of the experiment.

In Group A there were thirteen cats (Table I). No anatomic changes in the myocardium were observed, and the electrocardiographic alterations were not constant. Studies of the RS-T segments and T waves in approximately 250 electrocardiograms (each with three leads) revealed the following: (1) no significant change; (2) positive T_3 changed to negative T_3; (3) negative T_3 changed to positive T_3; (4) decrease of height of T wave in one or more leads; (5) increase of height of T wave in one or more leads.

There were slight increases or decreases in the height of the T waves in the majority of the animals which received calculated therapeutic doses of digitalis, but the changes recorded in Table I are only those

TABLE I

CORRELATION OF THERAPEUTIC DOSE OF DIGITALIS, DURATION OF THE EXPERIMENT, AND THE MOST PROMINENT CHANGE IN THE RS-T SEGMENT AND T WAVE, GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	20	Single dose, intravenous	14	Increase in height of T_1, T_2, T_3
Digalen	20	Single dose	15	No significant changes
Digalen	30	Single dose	6	No significant changes
Lanatoside C	30	Single dose	11	Slight decrease in height of T_3
Digitoxin	30	Single dose	11	Decrease in height of T_1; negative T_3 became positive
Lanatoside A	30	Single dose	12	Decrease in height of T_1 for 24 hr.; then increase in height of T_1, T_2, and T_3
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12	Negative T_3 became positive
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12	Negative T_3
Digalen	30	Single dose, intravenous	14	Increase in height of T_1, T_2, T_3
Digitoxin	30	Single dose, intravenous	14	Decrease in height of T_1 and negative T_3
Lanatoside A	30	Single dose, intravenous	18	No significant change
Lanatoside A	30	Single dose, intravenous	21	Negative T_3
Digifortis	30	Single dose, oral	56	Slight decrease in height of T_1 and T_2 for a few days

which were more or less prominent. Significant elevation or depression of the RS-T segment was not observed in any of the animals in Group A.

In Group B there were eleven cats (Table II). In these animals, which received a therapeutic dose of digitalis, plus estimated daily maintenance quantities of the drug, there were likewise no demonstrable myocardial lesions and no consistently typical electrocardiographic changes. Studies of the RS-T segments and T waves in approximately 350 electrocardiograms (each with three leads) revealed the following: (1) no significant change; (2) positive T_3 changed to negative T_3; (3) negative T_3 changed to positive T_3; (4) decrease of height of T waves in one or more leads; (5) increase of height of T waves in one or more leads.

In both Groups A and B, changes of cardiac rhythm were observed (no significant change, tachycardia, or bradycardia), but they were difficult to evaluate. Under the conditions of our experiments, even with the well-trained cats, cardiac rate did not seem to be a reliable index to the quantity of drug which the animal had received.

TABLE II

CORRELATION BETWEEN DOSAGE OF DIGITALIS, DURATION OF THE EXPERIMENT, AND MOST PROMINENT CHANGE IN RS-T SEGMENT AND T WAVE

The animals were digitalized with a calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose), and then given a daily dose of digitalis to correspond to either 1 or 2 cat units daily for a man weighing 70 kg.

GROUP B

DRUG USED	EQUIVALENT DAILY MAINTENANCE DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	MOST PROMINENT RS-T AND T CHANGE OBSERVED
Digalen	1	Intravenous	19	No significant change
Digifortis	1	Oral	19	Negative T_3 became positive
Digifortis	1	Oral	30	No significant change
Digalen	1	Intravenous	34	Negative T_3
Lanatoside A	1	Intravenous	36	No significant change
Digiglusin	2	Intravenous	20	Negative T_3; decrease in height of T_1
Digifortis	2	Oral	30	No significant change
Digalen	2	Intravenous	30	Tall T waves
Lanatoside A	2	Intravenous	36	Negative T_3
Digalen	2	Intravenous	40	Negative T_3
Digifortis	2	Oral	60	No significant change

Sinus arrhythmia, prolongation of the P-R interval, and shortening of the Q-T interval were observed in some of the animals. No ventricular premature contractions were noted in any of the electrocardiograms of the animals in Group A or Group B.

All of the electrocardiographic changes in Group A and Group B were reversible. The changes in the RS-T segment and T wave listed in Tables I and II constitute the predominant alteration during the period of observation. For example, in one case a negative T_3 developed six hours after 30 per cent of the minimal lethal dose of digitalis had been injected; this electrocardiographic change persisted for a few days and then disappeared.

C. Electrocardiographic Studies of Animals Which Received Toxic Doses of Digitalis.—It is difficult to group the animals in this series of experiments, for the dosage of digitalis and the intervals varied considerably. For convenience in presentation, the animals were arranged in two major groups: (1) Group A_1, those animals which received a single toxic dose of digitalis, had daily electrocardiograms (tracings were often made at hourly intervals on the day the drug was administered), and finally had the myocardium examined microscopically after varying periods; (2) Group B_1, those animals which received multiple doses of digitalis in various amounts over different periods, had daily electrocardiograms, and ultimately had their hearts subjected to histologic study.

Before the data are presented on these two major groups of animals, it might be well to point out again that in this section of the paper

TABLE III

CORRELATION OF SINGLE TOXIC DOSES OF DIGITALIS, DURATION OF THE EXPERIMENT, HISTOLOGIC STUDIES OF MYOCARDIUM, AND THE MOST PROMINENT CHANGES IN RS-T SEGMENT AND T WAVE

The changes in the RS-T segment and T wave are the most prominent which were observed during the course of the experiment; they do not represent the only change which occurred, or, necessarily, the final change. Many of the tracings returned to the control contour before the experiment was terminated.

GROUP A_1

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGE IN MYOCARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Digalen	40	Intravenous	12 days	No	Negative T_3; decrease in height of T_1 and T_2
Digiglusin	40	Intravenous	12 days	No	Negative T_3
Lanatoside A	40	Intravenous	12 days	No	Negative T_3; decrease in height of T_1 and T_2
Lanatoside C	50	Intravenous	11 days	No	Negative T_3
Digitoxin	50	Intravenous	13 days	No	Negative T_3; decreased height of T_1 and T_2; later, increased height of T_1, T_2, and T_3
Lanatoside A	50	Intravenous	14 days	No	Negative T_3
Digalen	50	Intravenous	15 days	No	Decreased height of all T waves, and then negative T_3
Digitoxin	60	Intravenous	12 hrs.	No	Decreased height of T_1 T_2, and T_3
Lanatoside C	60	Intravenous	9 days	No	
Lanatoside A	60	Intravenous	10 days	No	No significant change
Digitoxin	60	Intravenous	10 days	Yes	Elevation of RS-T_1, RS-T_2, and RS-T_3
Lanatoside C	60	Intravenous	11 days	Yes	No significant change
Digiglusin	60	Intravenous	12 days	No	Depression of RS-T_2 and RS-T_3
Digalen	60	Intravenous	14 days	No	Negative T_3
Digalen	60	Intravenous	15 days	No	Negative T_3
Lanatoside A	60	Intravenous	15 days	No	Negative T_3; depression of RS-T_1 and RS-T_2
Digitoxin	70	Intravenous	4 days	No	Depression of RS-T_1, RS-T_2, and RS-T_3
Lanatoside C	70	Intravenous	11 days	No	No significant change
Digiglusin	70	Intravenous	12 days	Yes	Depression of RS-T_1, RS-T_2, and RS-T_3 and then elevation of RS-T_1 and RS-T_2
Digiglusin	75	Intravenous	3 days	No	Slight elevation of RS-T_1, RS-T_2, and RS-T_3
Digiglusin	75	Intravenous	9 days	Yes	Negative T_3; elevation of RS-T_1 and RS-T_2
Lanatoside A	75	Intravenous	12 days	Yes	
Digiglusin	80	Intravenous	39 min.	No	Died, ventricular fibrillation

(Table continued on next page.)

TABLE III—CONT'D

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGE IN MYOCARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	80	Intravenous	3 hrs.	No	Died, ventricular fibrillation
Lanatoside A	80	Intravenous	4 hrs.	No	Died, ventricular fibrillation
Lanatoside A	80	Intravenous	6½ hrs.	No	
Digalen	80	Intravenous	1 day	No	
Lanatoside A	80	Intravenous	2 days	No	Depression of RS-T_1 and RS-T_2
Lanatoside A	80	Intravenous	3 days	No	Increased height of T_2 and T_3
Digalen	80	Intravenous	4 days	No	No significant change
Lanatoside A	80	Intravenous	5 days	Yes	Cove-plane, negative T_2 and T_3
Digitoxin	80	Intravenous	6 days	Yes	Elevation of RS-T_1 and RS-T_2
Lanatoside A	80	Intravenous	7 days	Yes	Elevation of RS-T_1 and RS-T_2
Lanatoside A	80	Intravenous	8 days	Yes	Elevation of RS-T_1 and RS-T_2; negative T_3 became positive
Lanatoside C	80	Intravenous	9 days	No	No significant changes
Lanatoside A	80	Intravenous	10 days	No	Decreased height of T_1, T_2, and T_3; slight depression of RS-T_1
Lanatoside A	80	Intravenous	10 days	Yes	Negative T_2; only few tracings
Lanatoside C	80	Intravenous	11 days	No	Elevation of RS-T_2 and RS-T_3 (not of plateau type)
Lanatoside A	80	Intravenous	12 days	Yes	Elevation of RS-T_1 and RS-T_2
Digalen	80	Intravenous	12 days	Yes	Decreased height of T_1; T_3 became positive; cove-plane, negative T_1, and positive T_2
Digiglusin	80	Intravenous	12 days	No	Striking depression of RS-T_1, RS-T_2 and RS-T_3
Lanatoside B	80	Intravenous	12 days	Yes	
Digitoxin	80	Intravenous	12 days	No	Increased height of T_1, T_2, and T_3
Tincture digitalis	80	Intravenous	12 days	Yes	Elevation of RS-T_1 and RS-T_2
Digifortis	80	Oral	13 days	Yes	Elevation of RS-T_2 and RS-T_3
Lanatoside A	80	Intravenous	14 days	Yes	Elevation of RS-T_1 and RS-T_2
Digalen	80	Intravenous	14 days	Yes	Elevation of RS-T_1, RS-T_2, and RS-T_3

TABLE III—CONT'D

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGE IN MYOCARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	80	Intravenous	16 days	Yes	Elevation of RS-T_1 and RS-T_2
Digalen	80	Intravenous	17 days	Yes	Cove-plane, negative T_2 and T_3; diphasic T_1
Lanatoside A	80	Intravenous	21 days	No	Negative T_3
Lanatoside A	80	Intravenous	23 days	Yes	Elevation of RS-T_1 and RS-T_2; negative T_3 became positive
Digalen	80	Intravenous	24 days	Yes	Elevation of RS-T_1 and RS-T_2
Digalen	80	Intravenous	30 days	Yes	Cove-plane, negative T_2 and T_3; positive T_1
Lanatoside A	80	Intravenous	30 days	Yes	Elevation of RS-T_1 and RS-T_2; normal electrocardiogram when killed
Digalen	80	Intravenous	42 days	Yes	Depression of RS-T_1, RS-T_3, and RS-T_2; then elevation of RS-T_2 and RS-T_3
Digalen	80	Intravenous	60 days	No	Negative T_3

we are dealing with toxic doses of digitalis and not with so-called therapeutic doses.

Table III summarizes the observations on the animals of Group A_1. The following are the various changes in the RS-T segments and T waves (Fig. 1) in more than 900 electrocardiograms (each with three leads) after different toxic amounts of digitalis had been administered as single doses: (1) no significant change; (2) positive T_3 changed to negative T_3; (3) decrease in height of T wave in one or more leads; (4) increase in height of T wave in one or more leads; (5) depression of the RS-T segment in one or more leads (6) cove-plane, negative T_2 and T_3, with positive or diphasic T_1; (7) cove-plane, negative T_1 and positive T_2 and T_3; (8) elevation of RS-T_1 and RS-T_2; (9) elevation of RS-T_2 and RS-T_3; (10) elevation of RS-T segment in all leads.

The following is an analysis of each of these electrocardiographic patterns in relation to the presence or absence of histologic changes in the mycardium.

Myocardial lesions were not found, as a rule, when there were no significant changes in the electrocardiograms. However, in one case myocardial lesions were present, but daily electrocardiograms failed to show any abnormality.

When a negative T_3 or a change in the height of the T wave constituted the only significant electrocardiographic abnormality, there was no demonstrable evidence of morphologic change in the myocardium.

The familiar depression of the RS-T segment (Figs. 1*f* and *g* and 2) in one or more leads was not associated with demonstrable histologic changes. If, however, this pattern was replaced by one in which the RS-T segment was elevated in two or more leads, myocardial lesions were observed.

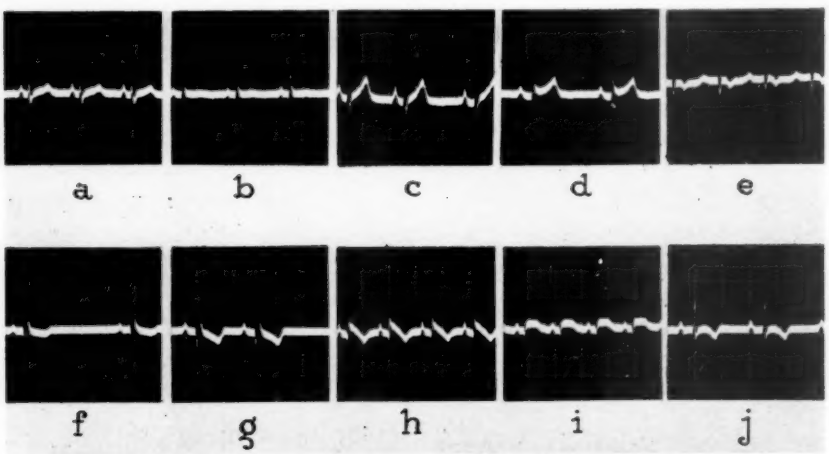


Fig. 1.—Electrocardiograms (all Lead II) selected to show the various types of changes which were observed after administration of toxic doses of digitalis: *a*, control; *b*, decrease in height of T wave (one or more leads); *c*, increase in height of T wave (one or more leads); *d*, slight elevation of RS-T segment (one or more leads); *e*, simple inversion of T wave (one or more leads, usually in Lead III); *f*, bowl-type of depression of the RS-T segment (one or more leads); *g*, angulated type of depression of RS-T segment (one or more leads); *h*, initial portion of RS-T segment above isoelectric position and terminal portion below isoelectric line; transition between *g* and *i* (one or more leads); *i*, plateau type of elevation of RS-T segment (one or more leads); *j*, cove-plane, negative T wave (Leads I and II or Leads II and III).

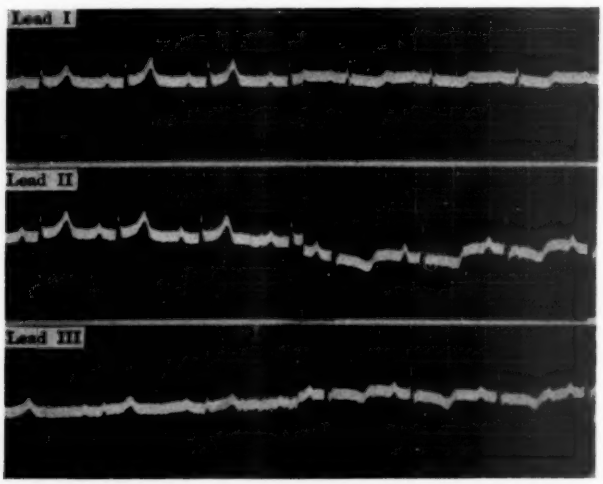


Fig. 2.—On the left, control electrocardiogram; on the right, depression of the RS-T segment after administration of a toxic dose of digitalis. Myocardial lesions were not associated with this pattern.

We observed several electrocardiographic patterns which were usually associated with myocardial histologic changes. The following is a list of these patterns: (1) elevation of RS-T_1 and RS-T_2; (2) elevation of RS-T_2 and RS-T_3; (3) elevation of RS-T_1, RS-T_2, and RS-T_3; (4) positive T_1 and cove-plane, negative T_2 and T_3; (5) cove-plane, negative T_1 and positive T_2 and T_3.

It is important to point out that the elevation of the RS-T segment must show certain characteristics if the foregoing statement is to be valid. Elevation of the segment must persist one to three days, and the segment must take off high on the R wave, pass along more or less horizontally, and then grade into the T wave, almost completely obliterating the ascending limb of the latter (Figs. 1*i* and 3). If the elevated segment exhibited a high take-off from the R wave but was followed by a distinct ascending limb of the T wave (Fig. 1*d*), myocardial lesions were seldom found; this pattern is usually transitory, and, in some cases, may be associated with metabolic changes in the myocardium which, if they persisted long enough, could be precursors of anatomic changes.[1, 33]

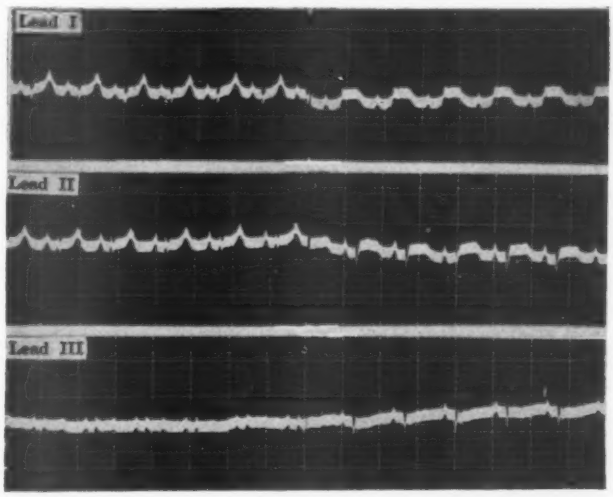


Fig. 3.—On the left, control electrocardiogram; on the right, "plateau type" of elevation of RS-T_1 and RS-T_2. Myocardial lesions were associated with this pattern.

Although, in these experiments, simple negativity of T_3 was not accompanied by myocardial lesions, cove-plane negativity of T_2 and T_3 was usually associated with histologic changes in the myocardium (Fig. 4). Again, this pattern must persist one to three days to make this statement valid.

The cove-plane, negative T_1 and positive T_3 pattern was observed definitely only once, and occurred in an animal which had histologic lesions in the myocardium.

One might wonder whether elevation of the RS-T segment in all leads was associated with acute exudative pericarditis. Animals in which this electrocardiographic pattern was observed did not show any gross signs of pericarditis. Subepicardial lesions might account for the electrocardiographic changes but specific investigations were not made to answer this question with certainty.

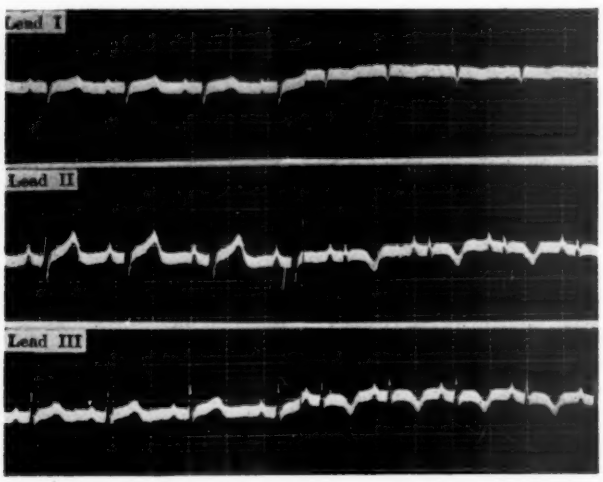


Fig. 4.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3. Myocardial lesions were associated with this pattern.

It should be emphasized that the changes in the RS-T segment and T wave recorded in Table III represent the most prominent alterations that were observed in the series of daily electrocardiograms on each animal. The contents of the table were simplified by eliminating comments on changes which were perhaps of minor importance for the solution of our problem (sinus tachycardia, sinus bradycardia, sinus arrhythmia, partial and complete heart block, ventricular premature contractions, coupling of beats, ventricular tachycardia, ventricular fibrillation, changes in the height and direction of the P wave, changes in the QRS complex, minor changes in the height of the T wave, and changes in the P-R and Q-T intervals). It could not be shown that these electrocardiographic alterations gave any clues to the presence or absence of demonstrable morphologic changes in the myocardium. A toxic dose of digitalis may produce all or any one of the foregoing changes within the course of a few hours, and even cause the death of the animal; yet no demonstrable myocardial lesions can be found. On the contrary, these electrocardiographic changes may be observed at various times during the course of daily observations on animals which have received toxic doses of digitalis. For example, complete heart block or ventricular fibrillation may develop one hour after the administration of a single toxic dose of digitalis, but there may not be

any demonstrable anatomic changes in the myocardium, or these two disturbances of rhythm may develop ten days after a single toxic dose of digitalis and there may be ample histologic evidence of changes in the myocardium. Therefore, it was necessary to rely on changes in the RS-T segment and T wave, rather than on any of the numerous electrocardiographic alterations listed in the former part of this paragraph, to give us hints about the histologic status of the myocardium after the administration of toxic doses of digitalis.

Before concluding our remarks on the electrocardiographic alterations produced by digitalis, it is of interest that the changes in the RS-T segment and T wave indicated in Table III did not persist indefinitely. The electrocardiogram frequently was observed to have returned to normal in those animals which were killed approximately between the tenth and twentieth day after the toxic dose of digitalis had been administered, although histologic evidence of inflammation was still present in the myocardial lesions, in which fibroblastic proliferation was beginning. Furthermore, the electrocardiogram had become entirely normal in all the animals in which the myocardial lesions were shown by microscopic examination to have healed.

The time of observation after the administration of any given toxic dose of digitalis is important in correlating the electrocardiographic changes with the histologic structure of the myocardium. A study of the limited amount of data included in Table III indicates the significance of this interval. If the animal had received a given toxic dose of digitalis and had been killed (or had died spontaneously) before sufficient time had elapsed for demonstrable histologic changes to develop, the electrocardiographic observations were different from those on animals which had been permitted to survive long enough for myocardial lesions to develop. Furthermore, if the interval was selected properly, the electrocardiogram might have returned to normal, although healing lesions, with active inflammatory components, were present in the myocardium. Finally, if the tracings were taken during the stage in which myocardial scars were present, the electrocardiogram was normal and there was no evidence in the tracing that the myocardium was filled with focalized zones of fibrosis.

Now let us turn to a consideration of the electrocardiographic changes in Group B_1, that is, in those animals which were digitalized with calculated therapeutic amounts of digitalis and then were given daily doses of digitalis in the estimated toxic range (daily doses to correspond to 3,4, 5.5, or 6 cat units; the body weight of the cat, in kilograms, and the weight of a 70-kilogram man were taken as the basis for these calculations). Group B_1 (Table IV) was composed of thirteen cats on which more than 250 electrocardiograms (each with three leads) were made. As in the foregoing Group A_1, it was found that elevation of the RS-T segments and cove-plane, negative T waves in Leads II and III were associated with myocardial lesions when these electrocardiographic

changes persisted one to several days. Depression of the RS-T segment was unassociated with myocardial lesions.

TABLE IV

CORRELATION OF DOSAGE OF DIGITALIS, DURATION OF THE EXPERIMENT, HISTOLOGIC STUDIES OF THE MYOCARDIUM, AND THE MOST PROMINENT CHANGES IN THE RS-T SEGMENT AND T WAVE

The animals were digitalized with a therapeutic dose (30 per cent of minimal lethal dose), and were then given daily quantities of digitalis estimated to correspond to 3, 4, 5.5, and 6 cat units daily for a man weighing 70 kg.

GROUP B_1

DRUG USED	EQUIVALENT DAILY MAINTENANCE DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES IN HEART	MOST PROMINENT CHANGE OBSERVED IN RS-T AND T
Digitoxin	3	Intravenous	5	Yes	Elevation of RS-T_2 and RS-T_3
Digifortis	3	Oral	11	Yes	Elevation of RS-T_1, RS-T_2, RS-T_3
Tincture digitalis	3	Intravenous	13	Yes	Elevation of RS-T_1 and RS-T_3
Tincture digitalis	3	Intravenous	14	No	Depression of RS-T_1, RS-T_2, RS-T_3
Tincture digitalis	3	Intravenous	18	No	Very slight elevation of RS-T_1 and RS-T_3
Lanatoside A	3	Intravenous	25	Yes	Elevation of RS-T_2 and RS-T_3
Lanatoside A	3	Intravenous	30	Yes	Elevation of RS-T_1 and RS-T_3
Digiglusin	4	Intravenous	7	Yes	Cove-plane, negative T_2 and T_3
Digifortis	4	Oral	14	Yes	Initial elevation and final depression of each RS-T segment in all leads
Digifortis	4	Oral	19	Yes	No significant change
Digifortis	4	Oral	30	Yes	Insufficient number of tracings
Lanatoside A	5.5	Intravenous	30	Yes	Cove-plane, negative T_2 and T_3
Digifortis	6	Oral	30	Yes	Elevation of RS-T_2 and RS-T_3

In one case, on the day on which the animal was killed the electrocardiogram showed an initial elevation and a terminal depression of each RS-T segment. That is, the segment began well above the isoelectric position and terminated well below it (Fig. 1*h*). This pattern was present in all leads. The myocardium of this animal was found to have recent degenerative lesions. This electrocardiographic pattern was observed several times in animals in group A_1; it represents a transitional stage between the depressed RS-T segment type (Fig. 1*g*) and the elevated RS-T segment type (Fig. 1*i*).

One animal in Group B_1 was found to have histologic changes in the myocardium, but no significant alterations were observed in any of the daily electrocardiograms.

COMMENT

The remarks made in the preceding paper[1] regarding the sources of error in the dosage of digitalis apply, of course, to these studies on the electrocardiographic changes after various amounts of the drug had been administered.

The electrocardiographic changes were variable, and there was a tendency for the tracing to revert to normal. It is likely that we may have missed some of the significant changes, for we made our electrocardiograms only once a day in the more prolonged experiments.

It should be kept in mind that the electrocardiographic changes which were described as indications of myocardial lesions were produced by doses of digitalis that were definitely toxic.

It should be pointed out that the electrocardiogram may be normal even though healing lesions, with histologic evidence of active inflammation, still persist in the heart. Therefore, the time at which the tracing is made is important.

The position of the animal must be defined if the electrocardiographic changes are to mean anything. For example, an animal treated with digitalis may have an elevated RS-T segment in Lead I and an isoelectric RS-T segment in Lead III while it lies on its right side, but these changes are reversed if the animal lies on its left side; that is, the RS-T segment becomes isoelectric in Lead I and elevated in Lead III.

Care was taken to avoid the technical errors which would result from incorrect standardization and poor contact between the animal's skin and the electrodes.

SUMMARY

Calculated therapeutic amounts (20 or 30 per cent of minimal lethal dose) of digitalis, in single doses, or in divided doses over a period of forty-eight hours, produced the following types of RS-T segment and T-wave changes: (1) No significant change; (2) positive T_3 changed to negative T_3; (3) negative T_3 changed to positive T_3; (4) decrease of height of T wave in one or more leads; (5) increase of height of T wave in one or more leads.

Similar electrocardiographic patterns were noted when animals were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given daily doses which were estimated to be equivalent to 1 or 2 cat units a day for a 70-kilogram man. The electrocardiographic studies were made during experiments which lasted from six to fifty-six days.

Myocardial lesions were not observed in any of these two groups of animals.

In our experiments there were no constant changes in the RS-T segment or T wave which could be taken as a reliable index to the presence of a calculated therapeutic amount of digitalis. The cardiac rate was also unreliable; a therapeutic dose of digitalis produced an increase, decrease, or no change in the cardiac rate over a period of days.

Toxic amounts of digitalis, when administered in single doses (40 to 80 per cent of the minimal lethal dose), or when given daily to digitalized animals in an amount which corresponded to 3,4, 5.5, or 6 cat units for a 70-kilogram man, produced the following electrocardiographic alterations: (1) no significant change; (2) positive T_3 changed to negative T_3; (3) decrease of height of T wave in one or more leads; (4) increase of height of T wave in one or more leads; (5) depression of the RS-T segment in one or more leads; (6) change in the RS-T segment, the initial portion of which began above the isoelectric position and the terminal portion of which ended below the isoelectric line; (7) elevation of the RS-T segment ("plateau type") in one or more leads; (8) cove-plane, negative T_2 and T_3, with positive T_1; (9) cove-plane, negative T_1 and positive T_2 and T_3.

Changes (1) to (5), inclusive, were usually not associated with myocardial lesions, whereas patterns (6) to (9) were associated with myocardial lesions produced by digitalis.

Two animals that had microscopic evidence of myocardial lesions failed to show any significant changes in the daily electrocardiograms.

The electrocardiogram returned to normal in all animals which did not die spontaneously or were not killed for experimental reasons.

The electrocardiograms returned to normal while microscopic evidence of active inflammation persisted in the myocardium.

The electrocardiogram was normal in those animals in which the myocardial lesions had healed (focalized zones of fibrosis).

REFERENCES

1. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. I. Effects on the Myocardial Cellular Structure, AM. HEART J. 25: 648, 1943.
2. Nicolai, G. F., and Simons, A.: Zur Klinik des Elektrokardiogramms, Med. Klin. 1: 160, 1909.
3. Straub, H.: Der Einfluss von Strophanthin, Adrenalin und Muskarin auf die Form des Elektrokardiogramms, Ztschr. f. Biol. 53: 106, 1909.
4. Selenin, W. P.: Das Elektrokardiogramm und die pharmakologischen Mittel aus der Gruppe des Digitalins und des Digitoxins, Arch. f. d. ges. Physiol. 143: 137, 1912.
5. Bickel, A., and Tsividis, A.: Ueber den Einfluss der Digitaliskörper auf die Kurve des Elektrokardiogramms, Biochem. Ztschr. 45: 462, 1912.
6. Bickel, A., and Pawlow, M.: Ueber den Einfluss einiger Herzmittel auf die Kurve des Elektrokardiogramms, Biochem. Ztschr. 48: 459, 1913.
7. Rothberger, C. J., and Winterberg, H.: Ueber den Einfluss von Strophanthin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens, Arch. f. d. ges. Physiol. 150: 217, 1913.
8. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. 21: 593, 1915.
9. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, With Especial Reference to A-V Conduction, J. Exper. Med. 23: 613, 1916.

10. Robinson, G. C., and Wilson, F. N.: A Quantitative Study of the Effect of Digitalis on the Heart of the Cat, J. Pharmacol. & Exper. Therap. **10**: 491, 1918.
11. Harris, I., and Edin, S.: Electrocardiographic Depression Produced by Digitalis, Lancet. **1**: 464, 1918.
12. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**: 244, 1920.
13. Pardee, H. E. B.: The Standardization of Digitalis by Its Action on the Human Heart, J. A. M. A. **81**: 186, 1923.
14. McCulloch, Hugh, and Rupe, W. A.: Studies on the Dosage of Digitalis in Children, Am. J. M. Sc. **162**: 231, 1921.
15. Marvin, H. M., Pastor, R. B., and Carmichael, M.: The Electrocardiogram and Blood Pressure During Surgical Operation and Convalescence: Effect of Routine Preoperative Digitalization, Arch. Int. Med. **35**: 782, 1925.
16. DeGraff, A. C., and Wible, C. L.: Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **24**: 1, 1926.
17. Yacoel, J., and Papapanayotou, D.: Des modifications électrocardiographiques sous l'influence de la digitale et de l'ouabaine, Arch. d. mal. du coeur. **20**: 24, 1927.
18. Cohn, A. E., and Stewart, H. J.: The Relation Between Cardiac Size and Cardiac Output Per Minute Following the Administration of Digitalis in Normal Dogs, J. Clin. Investigation **6**: 53, 1928.
19. Kahlson, G.: Beitrag zur Diagnose der Herzmuskelschwäche, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**: 421, 1928.
20. Brams, W. A.: The Effect of Digitalis on the Electrocardiogram: an Experimental Study on Dogs and Cats, Arch. Int. Med. **43**: 676, 1929.
21. Brams, W. A., and Gaberman, Peter: The Effect of Digitalis on the T-Wave of the Electrocardiogram: an Experimental Study in Human Beings, AM. HEART J. **6**: 804, 1931.
22. Schwartz, S. P., and Weiss, M. M.: Digitalis Studies on Children With Heart Disease; the Effects of Digitalis on the Electrocardiograms of Children With Rheumatic Fever and Chronic Valvular Heart Disease, Am. J. Dis. Child. **38**: 699, 1929.
23. Blumenfeldt, Ernst, and Strauss, S. G.: Der Einfluss der Digitalis auf die Finalschwankung des Elektrokardiogramms, Ztschr. f. klin. Med. **113**: 502, 1930.
24. Grünbaum, F.: Kontrolle der Digitalisbehandlung durch das Elektrokardiogramm, Ztschr. f. klin. Med. **116**: 746, 1931.
25. Bromer, A. W., and Blumgart, H. L.: The Maintenance Dose of Digitalis: an Electrocardiographic Study, J. A. M. A. **92**: 204, 1929.
26. Larsen, Kaj, Neukirch, Fritz, and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, AM. HEART J. **13**: 163, 1937.
27. Herles, F.: Einfluss der Digitalis auf das Elektrokardiogramm, Ztschr. f. Kreislaufforsch. **23**: 485, 1931.
28. Winternitz, Max: Der Einfluss der Digitalisdroge auf den Kammerkomplex des insuffizienten menschlichen Herzens, Ztschr. f. klin. Med. **119**: 632, 1932.
29. Bauer, Hellmut: Zur Kenntnis der Ursachen der Kumulierungserscheinungen der Digitalisglykoside. Ergebnisse physiologischer Methoden, Arch. f. exper. Path. u. Pharmakol. **172**: 699, 1933.
30. Korth, C., and Spang, K.: Die Wirkung des Digitoxins auf Elektrokardiogramm und Herzmuskel der Katze, Arch. f. exper. Path. u. Pharmakol. **184**: 349, 1937.
31. Spang, K., and Korth, C.: Die Wirkung des Digitoxins auf Elektrokardiogramm und Herzmuskel der Katze, Arch. f. exper. Path. u. Pharmakol. **188**: 690, 1938.
32. Bauer, H., and Reindell, H.: Zur Kenntnis der Ursachen der Kumulierungserscheinungen der Digitalisglykoside. Verlauf einer Digitoxinvergiftung, Arch. f. exper. Path. u. Pharmakol. **190**: 461, 1938.
33. Dearing, W. H., Barnes, A. R., Boothby, W. M., and Essex, H. E.: Unpublished data.

THE VASOCONSTRICTOR AND ANGIOTONIN-NEUTRALIZING PROPERTIES OF RENAL VENOUS PLASMA

HARRY WEINSTEIN, M.D., MEYER FRIEDMAN, M.D., H. L. NEWMAN, A.B., AND JEROME SUGARMAN, M.D.
SAN FRANCISCO, CALIF.

INTRODUCTION

HOUSSAY and Taquini,[1, 2] using the Läwen-Trendelenburg perfusion technique in the toad, demonstrated that the venous blood from the ischemic kidneys of dogs rendered hypertensive by constriction of the renal arteries contained a strong vasoconstrictor substance which was not present in the plasma obtained from venous blood of normal kidneys or in the plasma from systemic blood. Blood plasma from other organs to which the arterial supply had been partially reduced did not contain such a vasoconstrictor substance. Taquini[3, 4] and Prinzmetal and his associates[5] also found a marked vasoconstrictor or pressor substance in the venous blood from kidneys which had been completely ischemic for five to seven hours.

Numerous investigators[6-10] have demonstrated that acute constriction of the renal artery of a few minutes' duration is sufficient to produce a pressor substance in the venous blood of previously normal kidneys. Page and Helmer[11] were able to isolate a crystalline substance (angiotonin) from the interaction of renin and blood plasma which they believed was the effective pressor agent in the blood of hypertensive animals. Braun-Menéndez and his associates[9] have also described a pressor substance which appears to be identical with angiotonin. These investigators discovered also that this pressor substance could be neutralized by normal blood plasma. It was later found[12] that this neutralizing effect was diminished in blood from a kidney in which the arterial flow and pressure had been greatly reduced, as compared with that of blood from a systemic artery.

In the present communication we report the results of a study of the venous blood plasma from kidneys in which the arterial pressure and flow had been markedly reduced with respect to (1) its vasoconstrictor properties and (2) its content of angiotonin neutralizer.

METHODS

The Läwen-Trendelenburg perfusion technique was employed, using the California toad, *Bufo boreas kalophilus*, as the test animal. Briefly, the method consisted of perfusing a toad under constant pressure, first with Ringer's solution

From The Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, California.
Aided by a grant from the Dazian Foundation for Medical Research.
Received for publication Aug. 5, 1942.

containing 0.5 per cent sodium citrate, and then with the test solution, the basic portion of which was also Ringer's solution containing 0.5 per cent citrate. The toad was perfused with the control Ringer's solution until a constant perfusion rate was obtained, and then the test solution was allowed to run into the preparation. The drops flowing from the toad preparation during the control and the test period were counted. The decrease in the number of drops during perfusion with test solution, divided by the rate of the control perfusate, was recorded, and this percentage figure was used to express the activity or relative potency of the test substance as a vasoconstrictor.

Blood was collected from a kidney in which the arterial blood pressure and blood flow were markedly reduced, at a rate of 5 to 10 c.c. per minute over a fifteen- to thirty-minute period, from normal, anesthetized (pentobarbital sodium), heparinized dogs by a method previously described.[10] The blood flow through the kidney in these experiments was reduced approximately 90 to 95 per cent, and the renal arterial pressure was also markedly reduced. For control purposes, blood was also obtained from the brachial or jugular veins, and from the renal veins of normal kidneys. In all instances heparin was used as the anticoagulant, and the plasma obtained by centrifugation was then diluted with Ringer's solution containing 0.5 per cent citrate.

The following abbreviations will be used in the ensuing text to designate the various types of plasma:

1. D.K.P.—Venous blood plasma from a kidney in which arterial pressure and blood flow were markedly reduced.
2. N.K.P.—Venous blood plasma from a normal kidney.
3. N.V.P.—Normal, systemic, venous blood plasma.

TABLE I

THE VASOCONSTRICTOR EFFECT OF N.V.P. AND D.K.P.

EXP. NO.	CHANGE IN RATE OF OUTFLOW (PER CENT)	
	PERFUSION WITH D.K.P. (12.5 c.c.)*	PERFUSION WITH N.V.P. (12.5 c.c.)*
1	−50	−63
2	−76	+19
3		−18
4	−79	
5	−80	−39
6	−74	
7	−64	
8	−80	
9	−36	−33
10	−66	− 6
11	−60	
12	−80	−11
13		−11
14	−77	−29
15	−76	−20
Av.	−69	−26

*Diluted with Ringer's solution to 100 c.c.

RESULTS

A.—*The Vasoconstrictor Effect of D.K.P.*—Thirteen different samples of D.K.P. were diluted with Ringer's solution in the ratio of 12.5 c.c. of D.K.P. to 87.5 c.c. of Ringer's, or 1 part of D.K.P. to 8 parts of the total solution. When these D.K.P.-Ringer solutions were tested on the Läwen-Trendelenburg toad preparation (See Table I), employing a

fifteen-minute perfusion period, an average decrease of 69 per cent in rate of outflow was observed. Ten different samples of normal, systemic, venous blood plasma (N.V.P.), similarly diluted with Ringer's solution and perfused through the Läwen-Trendelenburg toad preparation, caused an average decrease in rate of flow of only 26 per cent. It is concluded, therefore, that D.K.P. possesses a significantly greater vasoconstrictor effect than does N.K.P.

B.—*The Angiotonin Neutralizing Content of D.K.P.*—In a previous report,[12] the limited ability of D.K.P. to neutralize the pressor property of angiotonin, as compared with that of normal, systemic, arterial blood plasma, was noted. It was thought desirable, also, to ascertain whether D.K.P. was similarly deficient in ability to neutralize the vasoconstrictor property of angiotonin, as compared with N.K.P. For this purpose, angiotonin* solution, as well as samples of D.K.P. and N.K.P. from thirteen normal dogs, was obtained, and the following mixtures were prepared:

1. 0.025 c.c. angiotonin (control).
2. 0.5 c.c. D.K.P. (control).
3. 0.025 c.c. angiotonin plus 0.5 c.c. of D.K.P.
4. 0.025 c.c. angiotonin plus 0.5 c.c. of N.K.P.
5. 0.025 c.c. angiotonin plus 0.2 c.c. of D.K.P.
6. 0.025 c.c. angiotonin plus 0.2 c.c. of N.K.P.

These mixtures were incubated for one hour at 38° C., then diluted to 100 c.c. in Ringer's solution containing 0.5 per cent citrate, and perfused through the Läwen-Trendelenburg toad preparation for a five-minute period.

TABLE II

THE NEUTRALIZATION OF ANGIOTONIN BY N.K.P. AND D.K.P.

EXP. NO.	CHANGE IN RATE OF OUTFLOW (PER CENT)					
	PERFUSION WITH ANGIOTONIN (0.025 C.C.)*	PERFUSION WITH D.K.P. (0.5 C.C.)*	PERFUSION WITH N.K.P. (0.5 C.C.) PLUS ANGIOTONIN (0.025 C.C.)*	PERFUSION WITH D.K.P. (0.5 C.C.) PLUS ANGIOTONIN (0.025 C.C.)*	PERFUSION WITH N.K.P. (0.2 C.C.) PLUS ANGIOTONIN (0.025 C.C.)*	PERFUSION WITH D.K.P. (0.2 C.C.) PLUS ANGIOTONIN (0.025 C.C.)*
1b	–73	–23	+ 4	– 9	–23	–49
2b	–66	+ 6	–26	–49	–38	–67
3b	–76	– 9	–21	–54	–21	–55
4b	–70	– 3	– 7	–21	–40	–49
5b	–61	– 3	–14	–44	–28	–44
6b	–70		– 5	–34	–23	–52
7b			– 8	–48	+ 2	–28
8b			+ 8	–23	–21	–34
9b			+ 2	–28	–13	–19
10b			– 5	–19	–21	–49
11b			–15	–41	–26	–24
12b			– 2	–20	– 8	–34
13b			– 8	–22		
Av.	–69	– 6	– 7	–32	–22	–42

*Diluted with Ringer's solution to 100 c.c.

*We are indebted to Irvine H. Page for the angiotonin solution used in these experiments.

Examination of the results (Table II) reveals that, whereas angiotonin alone, in the dilution used, effected an average decrease of 69 per cent in the rate of outflow from the Läwen-Trendelenburg preparation, the same quantity of angiotonin, first incubated with normal kidney blood plasma, lost almost all of its ability to affect the rate of outflow. However, the same quantity of angiotonin, if first incubated with D.K.P., still decreased the rate of outflow 32 per cent and 42 per cent, respectively, depending upon the quantity of D.K.P. used in the partial neutralization process. Obviously, therefore, D.K.P. did not neutralize the vasoconstrictor effect of angiotonin as well as did N.K.P.

SUMMARY

Our experiments showed that blood from a kidney in which the arterial flow and pressure had been markedly reduced possessed a greater vasoconstrictor effect and a lesser ability to neutralize angiotonin than did normal kidney blood.

REFERENCES

1. Houssay, B. A., and Taquini, A. C.: Acción vaso-contrictora de la sangre Venosa del rinón isquemiado, Rev. Soc. argent. de biol. **14**: 5, 1938.
2. Houssay, B. A., and Taquini, A. C.: Action Vaso-constrictrice du sang Veineux du rein ischémié, Compt. rend. Soc. de biol. **128**: 1125, 1938.
3. Taquini, A. C.: Liberación de substancia hipertensora en el rinón completamente isquemiado, Rev. Soc. argent. de biol. **114**: 570, 1939.
4. Taquini, A. C.: Production de substance hypertensive par le rein ischémié, Compt. rend. Soc. de biol. **130**: 459, 1939.
5. Prinzmetal, M., Lewis, H., and Leo, S.: Etiology of Hypertension Due to Complete Renal Ischemia, Proc. Soc. Exper. Biol. & Med. **43**: 696, 1940.
6. Enger, R., Linder, F., and Sarre, H.: Die Wirkung quantitativ abgestufter Drosselung der Nierendurchblutung auf den Blutdruck, Ztschr. f. d. ges. exper. Med. **104**: 1, 1938.
7. Verney, E. B., and Vogt, M.: Experimental Investigation Into Hypertension of Renal Origin With Some Observations on Convulsive "Uremia," Quart. J. Exper. Physiol. **28**: 253, 1938.
8. Braun-Menéndez, E., and Fasciolo, J. C.: Acción Vasoconstrictora e hipertensora de la sangre venosa del rinón en isquemia incompleta aguda, Rev. Soc. argent. de biol. **15**: 161, 1939.
9. Braun-Menéndez, E., Fasciolo, J. C., Leloir, E., and Munoz, J. M.: Substance Causing Renal Hypertension, J. Physiol. **98**: 283, 1940.
10. Friedman, M., Selzer, A., and Sampson, J. J.: Observations Concerning the Pressor Substance Present in the Ischemic Kidney Blood of the Dog, Am. J. Physiol. **131**: 799, 1941.
11. Page, I. H., and Helmer, O. M.: Crystalline Pressor Substance (Angiotonin) Resulting From Action Between Renin and Renin Activator, J. Exper. Med. **71**: 29, 1940.
12. Friedman, M.: Neutralization of Angiotonin by Normal and by Ischemic Kidney Blood Plasma, Proc. Soc. Exper. Biol. & Med. **47**: 348, 1941.

ACUTE RHEUMATIC FEVER AND VALVULAR DAMAGE

MORTON G. BROWN,* M.D.
BOSTON, MASS.

IN A NUMBER of studies[1, 2, 3] of rheumatic fever, it has been emphasized that the age of the patient at the onset of the disease, the number of attacks, and the character of the illness are important factors in the development of permanent valvular damage. The concept that factors inherent in the patient himself may be of equal or greater importance has received little attention. The present study is an attempt to evaluate the relative importance of the character of the disease, as opposed to the constitutional make-up of the patient, in determining the occurrence of permanent cardiac damage after rheumatic fever.

MATERIAL

The present analysis comprises two hundred fourteen patients with acute rheumatic fever who were admitted to the hospital during one or more attacks. After the acute attack, they were kept under observation in the outpatient department for a period of not less than four years, and for an average period of nine years. Most of them were examined personally for the final evaluation of their cardiac status. The observations were analyzed with regard to the occurrence or nonoccurrence of permanent cardiac damage in relation to the number and severity of attacks of rheumatic fever and the age at the time of the first attack. The latter was not considered in detail, but only in regard to puberty; the age of puberty was taken as thirteen years.

OBSERVATIONS

Ninety-nine patients, or 46 per cent, showed no clinical evidence of heart disease. Physical examination, the electrocardiogram, the teleoroentgenogram, and fluoroscopic examination were taken into consideration in arriving at this conclusion. This group is an extension of that previously reported.[4]

One hundred two patients, or 48 per cent, showed evidence of permanent valvular damage; adequate follow-up data could not be obtained in thirteen cases (6 per cent).

In the group with heart disease and in the group without heart disease, rheumatic fever appeared in single or multiple attacks before, after, or before and after, puberty (Table I). The incidence of permanent cardiac damage after multiple attacks was not higher than after single attacks in either the prepuberty or the postpuberty groups. Although the average age of the patients without heart disease (14.7 years) was slightly higher than that of those with heart disease (14.0

From the Medical Service, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.
Received for publication Aug. 12, 1942.
*Lieutenant-Colonel, M.C., A.U.S.

years), an analysis of Table I, in relation to puberty, reveals that advancing age was no bar to either recurrences of rheumatic fever or the development of heart disease, and that the incidence of heart disease in the older group was the same as in the younger.

TABLE I

ACUTE RHEUMATIC FEVER

214 CASES

ONSET	NO HEART DISEASE		HEART DISEASE		NO FOLLOW-UP	
	NO.	%	NO.	%	NO.	%
Single attacks before puberty	30	14	11	5		
Multiple attacks before puberty	17	8	18	8		
Multiple attacks before and after puberty	11–	5	32	15		
Single attacks after puberty	29	14	22	10		
Multiple attacks after puberty	12	5	19	10		
Total	99	46	102	48	13	6

There were no discernible differences in the clinical characteristics of the rheumatic fever as far as the two groups were concerned. The severity and the duration of the disease, the electrocardiographic changes, and the incidence of pericarditis were similar.

Patients who show no permanent cardiac damage after the first attack of rheumatic fever are likely to escape permanent injury despite further attacks. Contrariwise, when patients developed heart disease, all of the valvular damage was evident after the first attack (Table II). The only relatively common exception was the late appearance of aortic stenosis.

TABLE II

APPEARANCE OF HEART DISEASE IN RELATION TO ATTACKS OF RHEUMATIC FEVER

102 CASES

	NUMBER OF CASES	PERCENTAGE
After first attack	52	51
At second attack	16	16
Before first known attack	18	17
Not known	16	16
Died of rheumatic fever, 11 patients Died of subacute bacterial endocarditis, 3 patients		

It is also to be noted that in the group with heart disease there were eleven deaths from acute rheumatic fever and three deaths from subacute bacterial endocarditis. No patient without evidence of valvular deformity died of acute rheumatic fever or bacterial endocarditis.

COMMENT

We have already called attention to the fact that the character of the rheumatic fever among the patients who recovered without permanent heart disease was no different from that among others. In this study we have shown that recurrences are equally frequent in both groups, and

do not bring about a higher incidence of heart disease. The age of the patient at the time of single or multiple attacks had nothing to do with the development of heart disease.

The fact that patients who show no permanent cardiac damage after the first attack of rheumatic fever are likely to escape it entirely has been observed before.[4, 5] The apparent exception to this rule in the case of patients who develop aortic stenosis many years after an attack of rheumatic fever may be explained by the manner in which this lesion develops.

The fact that only patients with demonstrable valvular disease die of acute rheumatic fever or bacterial endocarditis is important prognostically, and has already been pointed out by others.[6] It would thus appear that the life history of the disease is determined by the patient, and not by the severity, frequency, or character of the acute rheumatic attacks. It is impossible to state whether this represents an instance of specific resistance on the part of the heart, or whether there is a general immunologic reaction which alters the effect of rheumatic fever on the heart. It seems that the immunity of the host must play an important role, inasmuch as the patient who develops heart disease is the patient who may die of rheumatic fever, and the person who can resist the development of valvular damage does not die of rheumatic fever.

CONCLUSIONS

1. There is no relationship between the character of rheumatic fever, the number of recurrences, and the age of the patient at onset, on the one hand, and the development of cardiac damage, on the other hand.
2. Patients who develop valvular damage usually do so after the first attack of rheumatic fever.
3. The patient's immunity or resistance is the important factor in determining whether or not permanent valvular damage will develop.

REFERENCES

1. Bland, Edward F., and Jones, T. Duckett: The Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. 113: 1380, 1939.
2. Wilson, May G.: Rheumatic Fever, London, 1940, Commonwealth Fund.
3. Levine, Samuel A.: Clinical Heart Disease, ed. 2, Philadelphia, 1940, W. B. Saunders Co.
4. Brown, Morton G., and Wolff, Louis: Recovery From Acute Rheumatic Fever Without Permanent Cardiac Damage, New England J. Med. 223: 242, 1940.
5. Boone, J. A., and Levine, S. A.: The Prognosis in Potential Rheumatic Heart Disease and Rheumatic Mitral Insufficiency, Am. J. M. Sc. 195: 765, 1938.
6. Bland, Edward F., and Jones, T. Duckett: Fatal Rheumatic Fever, Arch. Int. Med. 61: 161, 1938.

Clinical Reports

RECURRENT LARYNGEAL NERVE PALSY IN MITRAL STENOSIS

SAMUEL ALPERT, M.D.
BRONX, N. Y.

RECURRENT laryngeal nerve palsy is a relatively uncommon complication of mitral stenosis. In spite of the very lucid anatomic explanation of this phenomenon by Fetterolf and Norris,[1] in 1911, there are still many who harbor the erroneous impression that the lesion is caused by direct compression by an enlarged left auricle. These authors demonstrated that the dilatation of the left auricle and pulmonary vessels which results from mitral stenosis causes a crowding of the mediastinal structures at the base of the heart. The dilated left superior pulmonary artery is literally pushed up against the nerve as it runs between this vessel and the aorta in the region of the ligamentum arteriosum. They made the additional observation that the function of the nerve was not always abolished by actual destruction from pressure, but that the same amount of functional disturbance might arise from a neuritis consequent upon a degree of compression not sufficient to destroy the vitality of the nerve. King and his collaborators,[2] in a very interesting paper, discussed recurrent laryngeal nerve palsy in cases of left ventricular failure and in the absence of mitral stenosis. They pointed out that failure of the left ventricle increases the pressure in the pulmonary circuit. This causes dilatation of the left superior pulmonary artery, which is responsible for compression of the nerve.

The following case re-emphasizes these points in dramatic fashion.

CASE REPORT

The patient was a 45-year-old Scotch woman; she was admitted to the Medical Service of Lincoln Hospital on Jan. 19, 1937, because of mildly active rheumatic heart disease. She gave a history of cardiac disease of ten years' duration, during which period she had noted increasing dyspnea on effort, and had experienced recurrent attacks of bronchitis and occasional hemoptysis. Three years earlier she had had a complete, right-sided hemiplegia, from which recovery was practically complete. In the preceding two years her voice had become increasingly hoarse, and this disability had been associated with dysphagia of moderate severity.

Physical examination revealed a poorly nourished woman who was slightly dyspneic and cyanotic. She was unable to speak above a whisper. There were indications of very marked enlargement of the heart. At the apex there was a rumbling presystolic murmur, and a blowing diastolic murmur was heard over the aortic area.

From the Medical Service of Lincoln Hospital, Bronx, N. Y.
Received for publication April 19, 1941.

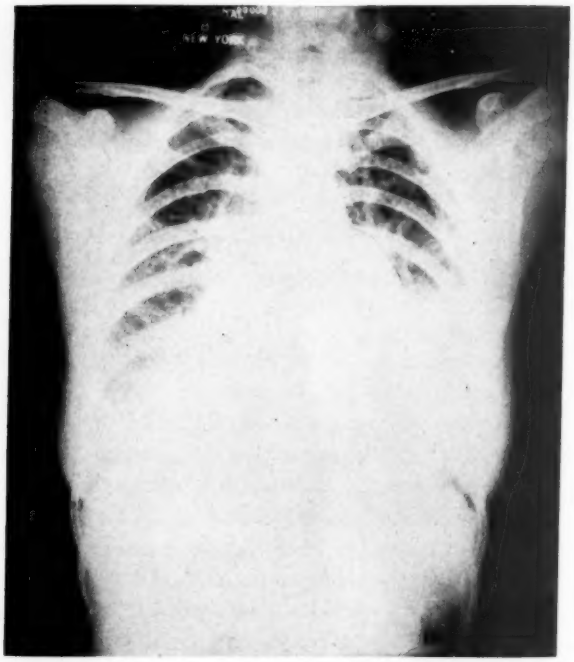


Fig. 1.—Teleoroentgenogram of chest, showing considerable enlargement of cardiac silhouette, with unusual prominence in region of pulmonic conus.

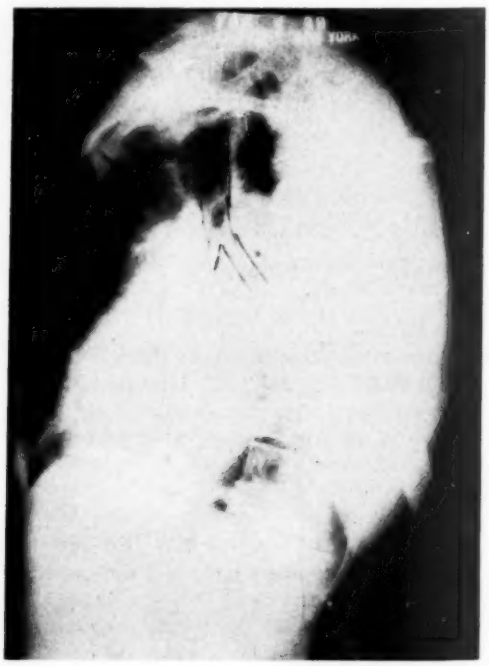


Fig. 2.—Left oblique anterior view, showing increased density of shadow cast by pulmonary artery beneath arch of aorta. The angle of bifurcation of the trachea remains unaltered, indicating absence of vertical enlargement of the left auricle.

The heartbeat was irregular. Residual evidence of the old hemiplegia consisted of exaggerated reflexes and ankle clonus on the right side. Examination of the larynx revealed adductor paralysis of the left vocal cord. Fluoroscopic and radiographic studies (Figs. 1, 2, 3) revealed pronounced enlargement in region of the outflow tract of the right ventricle, but no significant enlargement of the left auricle, either in a horizontal or vertical direction. The electrocardiogram showed marked right axis deviation and auricular fibrillation.

The patient had fever occasionally, usually associated with pain in the chest and exacerbation of the cough; these symptoms were variously interpreted as due to mild attacks of bronchopneumonia and pulmonary infarctions. After a prolonged stay in the hospital she was improved, and went home. However, she was compelled to return one week later because of increasing dyspnea and cough. This time her apparently favorable course was terminated rather suddenly by an acute pulmonary attack to which she succumbed.

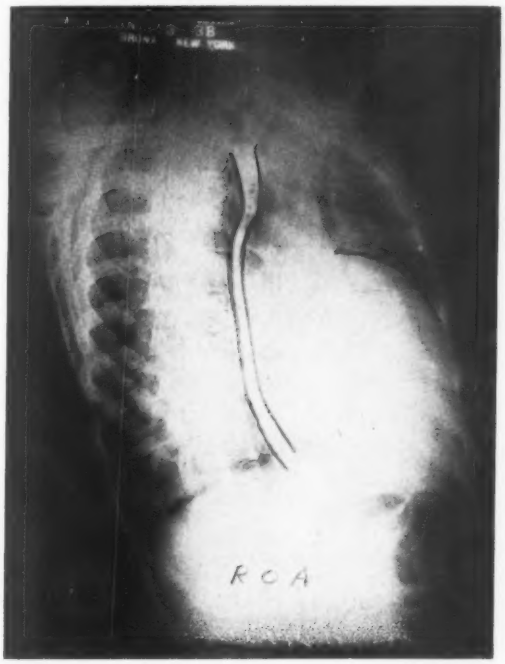


Fig. 3.—Right oblique anterior view, showing the striking prominence of the pulmonic conus, and a barium-filled esophagus pursuing a relatively straight course, indicating no enlargement of the left auricle in a horizontal direction.

Autopsy.—The heart weighed 450 grams, and presented evidence of damage to both mitral and aortic leaflets. The mitral orifice showed marked stenosis. The left auricle was not much dilated, but the wall of this chamber showed distinct hypertrophy. The pulmonary artery and its major branches showed enormous dilatation. Both the main stem and the left branch exceeded the aorta in circumference. The left recurrent laryngeal nerve was found in its usual situation between the aorta and the left pulmonary artery. Grossly, it appeared normal, with no evidence of compression. Microscopic examination, however, revealed advanced myelin degeneration. The left vocal cord was atrophic. The lungs showed evidence of marked chronic passive congestion and were the seat of bronchopneumonia.

COMMENT

The syndrome of pulmonary hypertension resulting from mitral stenosis, which this patient had, is well known. The constant dyspnea, repeated attacks of bronchitis, pulmonary infarction, right axis deviation, and, finally, bronchopneumonia, are all clinical expressions of increased tension in the pulmonary circuit. Also, the enlargement of the left superior pulmonary artery, which causes the compression of the left recurrent laryngeal nerve, represents the effect of this hypertension on the lesser circulation. It is important to note that the left auricle was not demonstrably enlarged, and therefore could not have compressed the nerve. The reason for the failure of the auricle to dilate is not clear. Whatever the cause may be, it appears that the pulmonary vascular system compensated for it by excessive dilatation. Another feature of interest was the absence of gross evidence of compression of the nerve, although, microscopically, there was ample evidence of a degenerative change comparable to the so-called neuritis described by Fetterolf and Norris.[1]

SUMMARY

A case of recurrent laryngeal nerve palsy complicating mitral stenosis is described; the nerve lesion was associated with marked pulmonary hypertension, which gave rise to considerable dilatation of the pulmonary artery and its major branches. The left auricle was not appreciably enlarged, and the suggestion is offered that the marked enlargement of the pulmonary vessels compensated for the failure of the auricle to dilate. Although there was no gross evidence of compression of the nerve, microscopic study revealed degenerative changes.

REFERENCES

1. Fetterolf, and Norris: The Anatomical Explanation of the Paralysis of the Left Recurrent Laryngeal Nerve Found in Certain Cases of Mitral Stenosis, Am. J. M. Sc. 141: 625, 1911.
2. King, Hitzig, and Fishberg: Recurrent Laryngeal Paralysis in Left Ventricular Failure, Am. J. M. Sc. 188: 691, 1934.

PUNCTURE WOUND OF THE LEFT AURICLE, WITH TAMPONADE AND RECOVERY

VERNE S. CAVINESS, M.D., AND HENRY G. TURNER, M.D.
RALEIGH, N. C.

J. S., a white man, aged 34 years, became severely intoxicated on the evening of May 9, 1937, engaged in a street brawl, and was stabbed in the left side of the chest. A passing police patrol car picked him up and carried him to Rex Hospital. The chief surgeon of the hospital (Dr. Turner) was ready to perform another emergency operation. After seeing this patient in the accident ward and recognizing the seriousness of the situation, the other operation was delayed so that J. S. might have immediate attention. He was taken to the operating room and the operation was started with a minimum of preparation in order to conserve time.

At that time the patient was in shock and only semiconscious. His skin was cold and clammy and he was perspiring freely. His pulse was imperceptible, and his blood pressure could not be measured. The heart rate was so rapid that it could not be counted with a stethoscope. There were at least two stab wounds in the left side of the chest; one was over the seventh rib, and another was about an inch higher. Both were in the midclavicular line. A diagnosis of heart tamponade was made.

When he was put on the operating table, hypodermoclysis with physiologic saline was begun. He was given a hypodermic injection of ¼ grain of morphine and $\frac{1}{150}$ grain of atropine. The anesthetic was ether. During the operation 1000 c.c. of 10 per cent glucose in physiologic saline were given intravenously.

The incision was made at the site of the stab wounds, and the sixth and seventh left costal cartilages were resected. The tip of the knife blade was removed from the seventh left costal cartilage. The pericardium was exposed and incised. It was tightly filled with blood and blood clots. These were removed, and the stab wound, from which blood was spurting, was located on the lateral aspect of the left auricle. The auricular wound was closed with 20-day, chromic catgut. The pericardium was lightly irrigated with physiologic saline solution, and was closed with fine, chromic catgut. The left lung was collapsed, and there was a moderate amount of bloody fluid in the chest. The fluid was removed, two small, rubber-tube drains were inserted, and the chest wall was closed in routine manner. During the operation the pulse rate gradually fell to 120 per minute, and the pulse volume became good.

When he was returned to his room, the pulse rate was 120 per minute and his blood pressure was 52/40. Recovery from the anesthetic was satisfactory.

The following day his general condition was much better. His pulse rate remained at about 120 per minute, but the pulse volume was greatly improved. His blood presure was 90/60. The heart sounds were faint. The drains were removed from the chest, and the opening was closed tightly. The following day his blood pressure was 105/60.

His postoperative rectal temperature was 104.2° F. There was a gradual fall in temperature until it reached normal on the tenth postoperative day. The temperature was slightly irregular for another week, but remained normal after that time. After the first week, his pulse rate ranged from 80 to 90 per minute. The respiratory rate was normal after the first week.

From the Surgical and Cardiovascular Departments, Rex Hospital, Raleigh, N. C.
Received for publication Jan. 2, 1942.

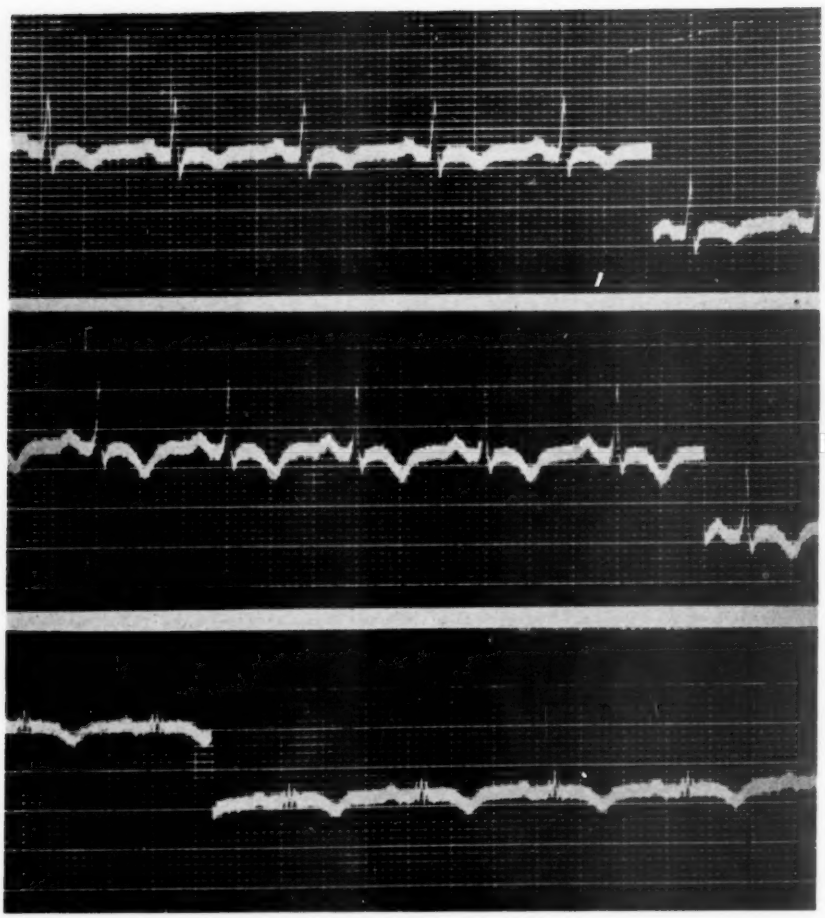


Fig. 1.—May 28, 1937; this tracing was made nineteen days after a puncture wound of the left auricle.

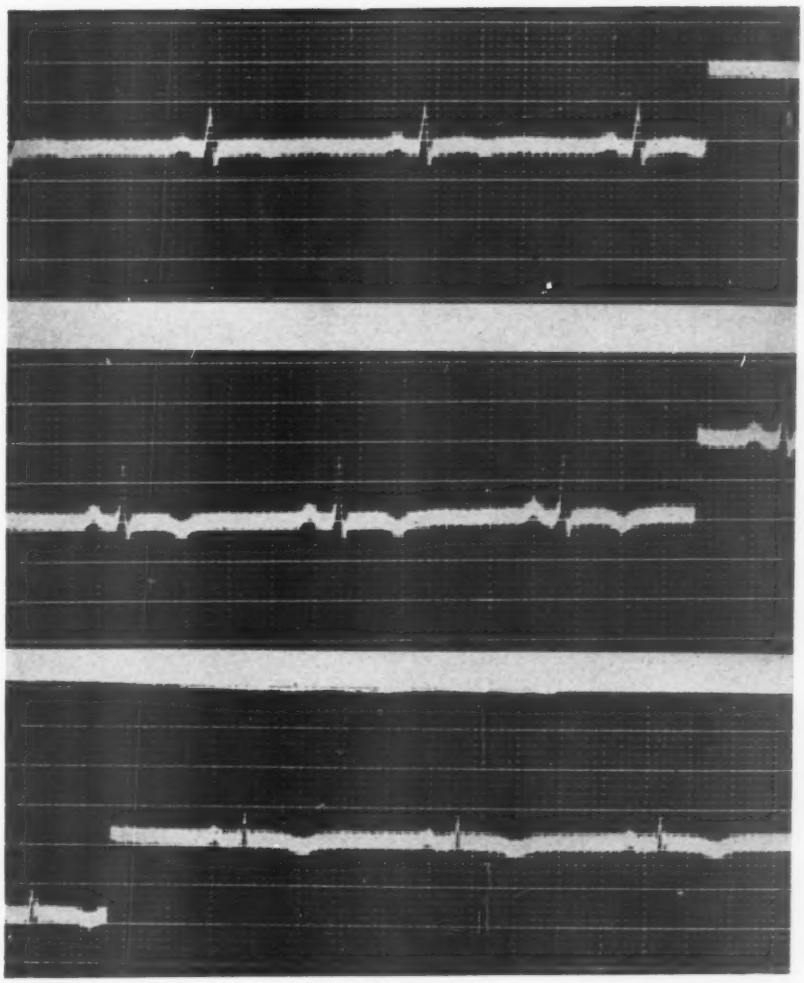


Fig. 2.—June 12, 1937.

The patient was never very anemic. During the first few weeks after the injury his hemoglobin was 70 per cent. Then it rose to 80 per cent, and has not changed appreciably since that time.

He appeared to have very little trouble on account of the collapsed left lung. A week after the injury, the left lung was generally hazy and there was slight pleural effusion. Two weeks later, the fluid was gone, and the lung was normal except for slight haziness over the base. After several weeks, the haziness in the base disappeared.

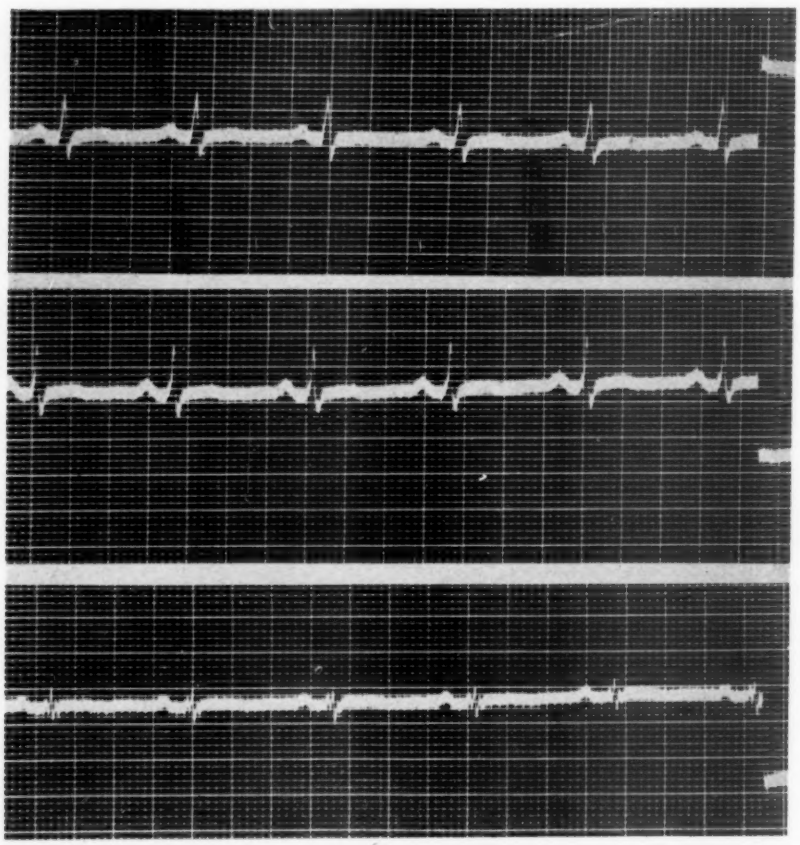


Fig. 3.—June 30, 1937.

When he was seen first by a medical consultant, May 28, 1937—nineteen days after the injury—the patient was quite ill. He was rather dusky in appearance, and had a rapid pulse and respiratory rate. His chest showed healing scars from the stab wounds and from the operation. There was a heaving precordial impulse, with intercostal retraction in systole. A thrill was felt at the apex in late diastole, and a rough murmur, beginning late in diastole and extending into systole, was heard at the apex. The apex beat was best heard and felt in the sixth left intercostal space, four inches to the left of the midsternal line. The heart rate was 100 per minute, and the heartbeat was regular and forceful; the sounds were generally roughened. The breath sounds were absent over the base of the left lung.

Fig. 4.—July 30, 1937.

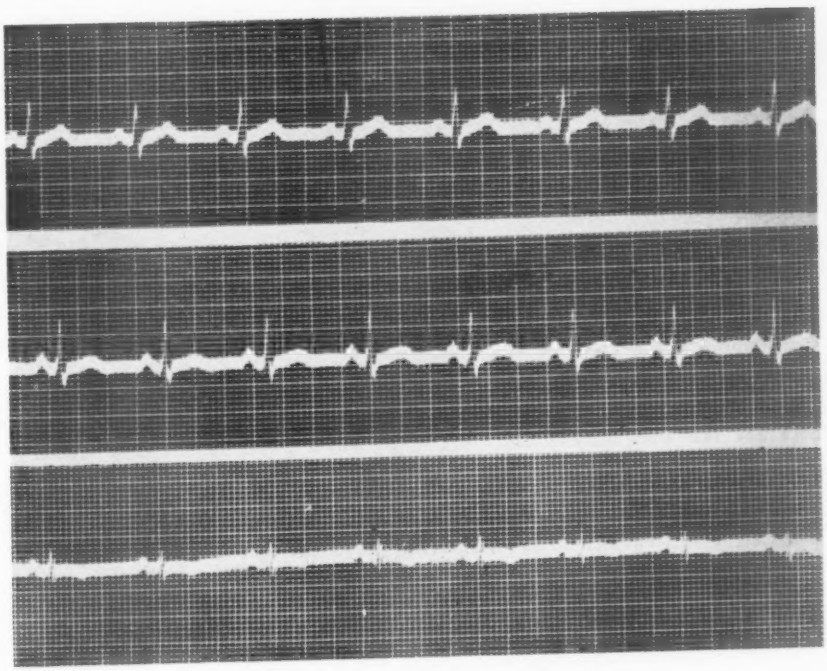


Fig. 5.—December 30, 1937.

The blood Wassermann reaction was negative. There was no history of syphilis or other serious illness. The patient had always been a laborer, and rarely ill. Physical examination showed nothing remarkable other than the injury.

The first electrocardiogram was made nineteen days after the injury (Fig. 1), and was like those which are often obtained after coronary occlusion. It showed normal rhythm, normal auriculoventricular conduction time (0.15 second), slight slurring of the QRS complexes, and negative T waves (Pardee type) in all leads. The P waves showed a slight diphasic tendency. The second tracing was made two weeks later, and showed a much slower rate and a definite return toward normal of the T waves in all leads (Fig. 2). There was no change in the P waves.

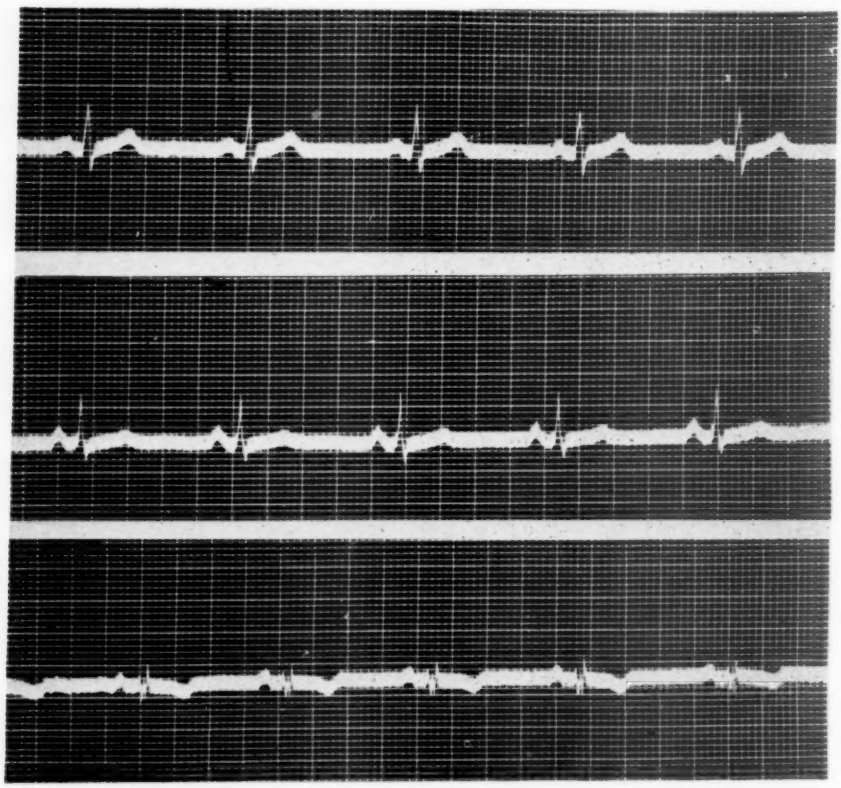


Fig. 6.—May 30, 1938.

Eighteen days later the tracing was almost normal in appearance, except for rather low amplitude of the T waves and some slurring of the QRS complexes (Fig. 3). There was still no change in the P waves. In tracings made a month later (Fig. 4), there was fair amplitude of the T waves in Leads I and II; in Lead III the T waves were almost isoelectric. The P waves were beginning to show improvement: in Lead I they were normal, and in Leads II and III they descended slightly lower after the upward thrust than before. In the later tracings (Figs. 5, 6, 7), as the patient's general condition improved, it will be noted that there was no change in the P waves, and that the diphasic tendency of P_2 and P_3 was still present; this tendency was observed in Lead IV. Also, T_3 became definitely negative.

During the first year after the injury, this man worked as a metal grader in a junk yard. This was heavy work, and at times he complained of dyspnea. Since

that time, except for periodic alcoholic debauches, he has been able to work regularly at anything he wished to do.

His blood pressure at the last reading was 144/90. That appears to be approximately his average pressure. His pulse rate has persistently remained in the eighties. The cardiac thrill and mitral murmurs have persisted; this suggests that he has an old rheumatic heart disease which was doubtless present before the injury occurred.

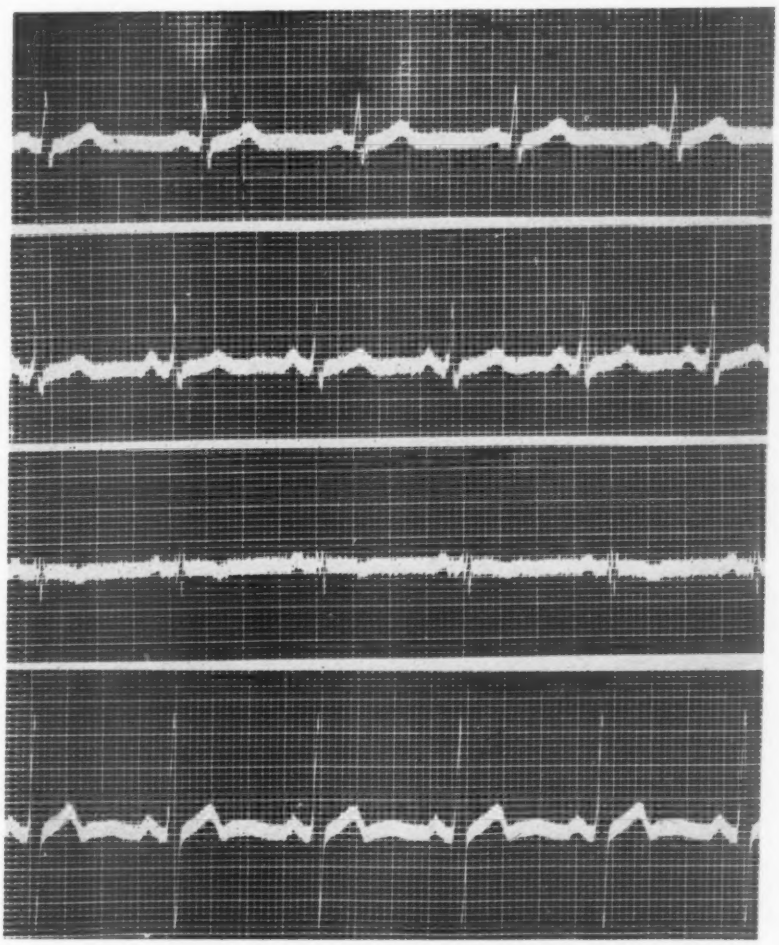


Fig. 7.—February 18, 1939.

CONCLUSIONS

A case of stab wound of the left auricle, with recovery, is reported.

The serial electrocardiograms suggest that electrocardiographic changes incident to injury of the auricles are not essentially different from those caused by injury of other portions of the myocardium, such as occurs after coronary occlusion. The P-wave changes were slight, and not like those ascribed to damage of the mitral valve.

AURICULAR FIBRILLATION OF LONG STANDING, WITH SPONTANEOUS RETURN TO NORMAL SINUS RHYTHM

MORRIS FOGEL, M.D.
AUGUSTA, GA.

IN REVIEWING the literature, only one case was found in which long-standing auricular fibrillation was replaced spontaneously by normal sinus rhythm. This case was reported by Burch,[1] in 1939; the auricular fibrillation had continued for twenty-two months and was succeeded by normal rhythm for a period of nine months. This was followed by a 9-month period of fibrillation, after which normal sinus mechanism was resumed and had continued for a period of four months, at which time the case was reported. Bishop[2] reported four cases of paroxysmal fibrillation; it is well established that, in such cases, normal sinus rhythm returns within a period of several hours to a week. Brill,[3] in a statistical review, stated that 90 per cent of paroxysms of fibrillation may continue for as long as one year and then cease spontaneously. It is commonly agreed that, once established, auricular fibrillation tends to persist throughout life. This case is the second of its kind to be reported. Normal sinus mechanism was resumed after a prolonged period of auricular fibrillation. The change took place spontaneously, without the aid of specific therapy.

CASE REPORT

W. C. B., a physician, aged 74 years, was admitted to the Veterans' Hospital Sept. 30, 1940, for the fourth time. His family history was noncontributory. The wife of the patient stated that she first knew that he had a cardiac ailment about fifteen years before; the exact nature of it she did not know. His personal physician, who examined him regularly prior to his first admission and between subsequent admissions, stated that he was certain that the patient had had a grossly irregular heartbeat for eleven years. His impression was that the irregularity had been present long before that, but he could not be sure because he had no exact records, and no electrocardiograms had been taken. The patient had been taking digitalis at irregular intervals.

He was first admitted on June 15, 1936, with a history of sudden, severe pain about the left kidney which was only partially relieved by barbiturates. The pain radiated to the end of the penis and to the inner aspects of both thighs. This was followed, in twenty-four hours, by bloodtinged urine and then by frank hematuria. He was admitted because of persistence of the pain. Physical examination revealed a well-nourished, 70-year-old white man who was afebrile. The pupils were

From the U. S. Veterans Facility, Biloxi, Mississippi.
Published with permission of the medical director, Veterans Administration, who assumes no responsibility for the opinions expressed.
Received for publication Jan. 26, 1942.

equal, circular, and regular in outline, and reacted readily to light and in accommodation. The ears, nose, and throat were essentially negative. Tenderness was elicited over the frontal sinuses, but further investigation failed to disclose any evidence of sinusitis. The chest was long, broad, and deep, and mobility was good

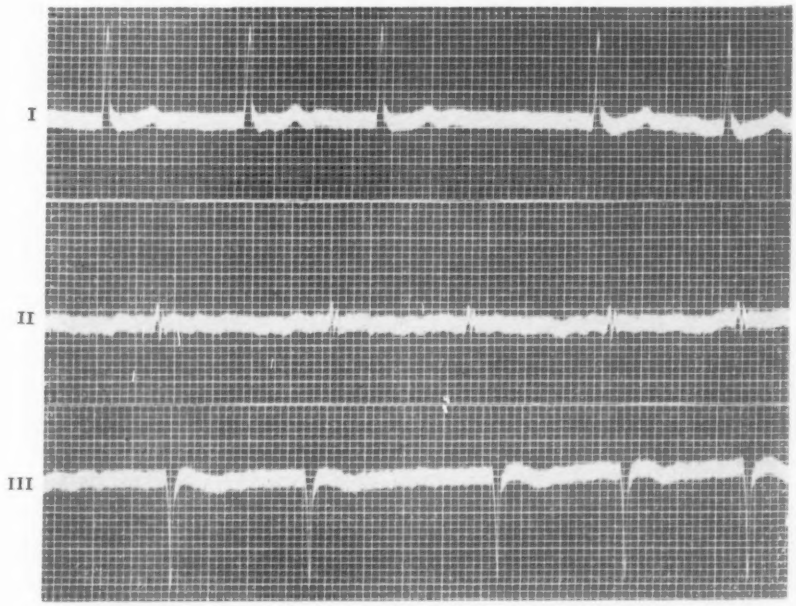


Fig. 1.—June 25, 1936.

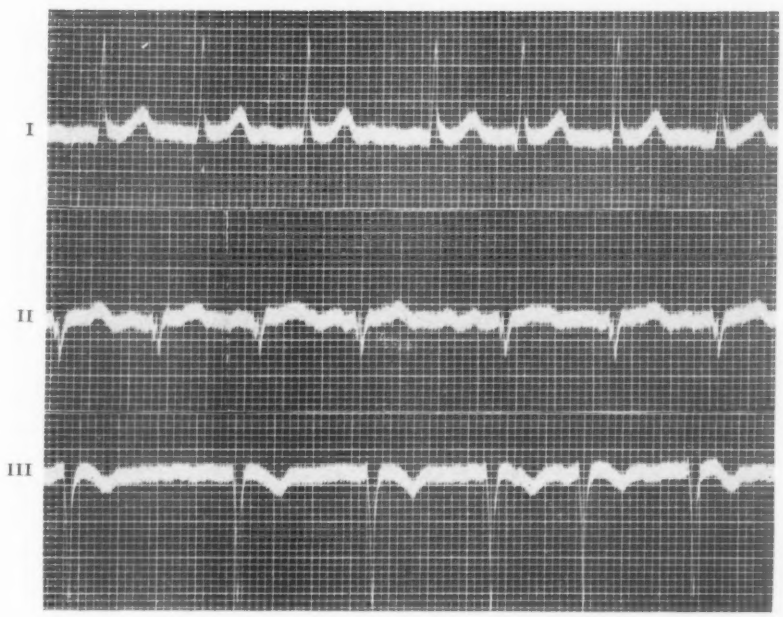


Fig. 2.—Dec. 15, 1938.

and equal on both sides. Expiration was somewhat prolonged and wheezy. No gross abnormalities of the lungs were found. Physical and roentgenologic examination disclosed no evidence of cardiac enlargement. The rate was rapid (108), and the beating was grossly irregular. The blood pressure was 148/102. No murmurs were heard. The abdomen was soft, and no masses were palpable. The liver was neither enlarged nor tender. Deep tenderness was elicited at the left costovertebral angle. Small external hemorrhoids were noted. No ankle or pretibial edema was present. The dorsalis pedis pulses were palpable. A blood cell count was not done. Urinalysis disclosed the presence of 3 or 4 erythrocytes per high-power field; these disappeared from the urine in two weeks. The serologic reactions were negative. An electrocardiogram (Fig. 1) disclosed evidence of myocardial damage, left axis deviation, and auricular fibrillation. He was kept on a maintenance dose of digitalis (1½ grains daily), and was discharged improved on June 29, 1936, with a diagnosis of renal infarction (embolic) secondary to arteriosclerotic heart disease and auricular fibrillation.

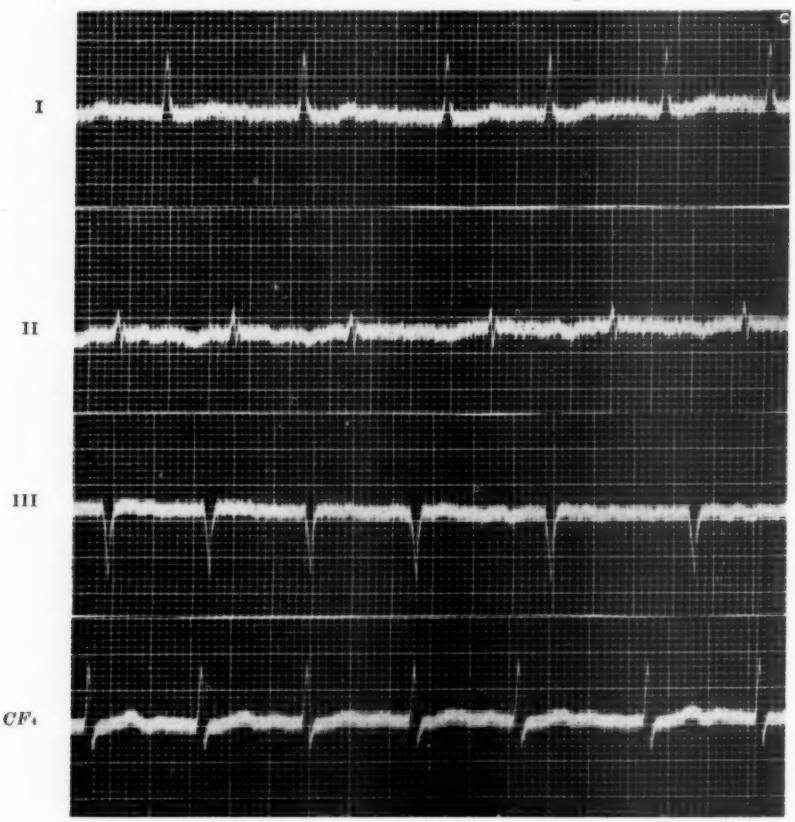


Fig. 3.—Nov. 8, 1940.

He was next seen on Dec. 10, 1938, when he was admitted with symptoms of an acute exacerbation of chronic cholecystitis. Cholecystograms disclosed a nonfunctioning gall bladder. In view of the age of the patient and his general condition, surgical treatment was not advised at that time, and he was treated symptomatically. The cardiac abnormalities were the same as they had been when the

patient was seen in 1936. Auricular fibrillation (Fig. 2) was still present, and the patient was still taking 1½ grains of digitalis daily. He was discharged improved on May 7, 1939.

On June 29, 1939, he was readmitted to have dentures fitted, but no record was made of his cardiac status because of his short stay in the hospital.

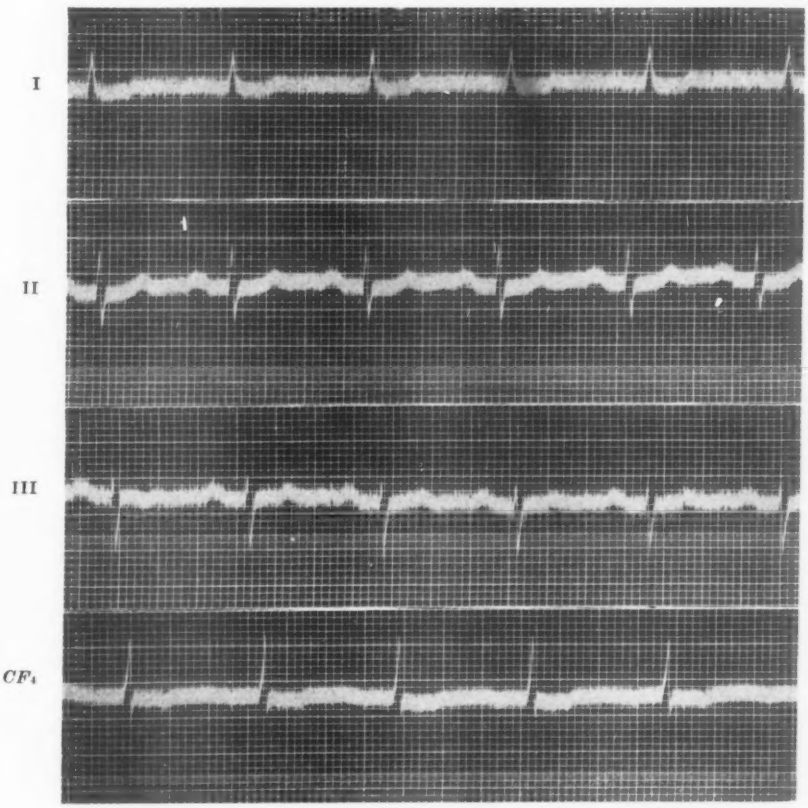
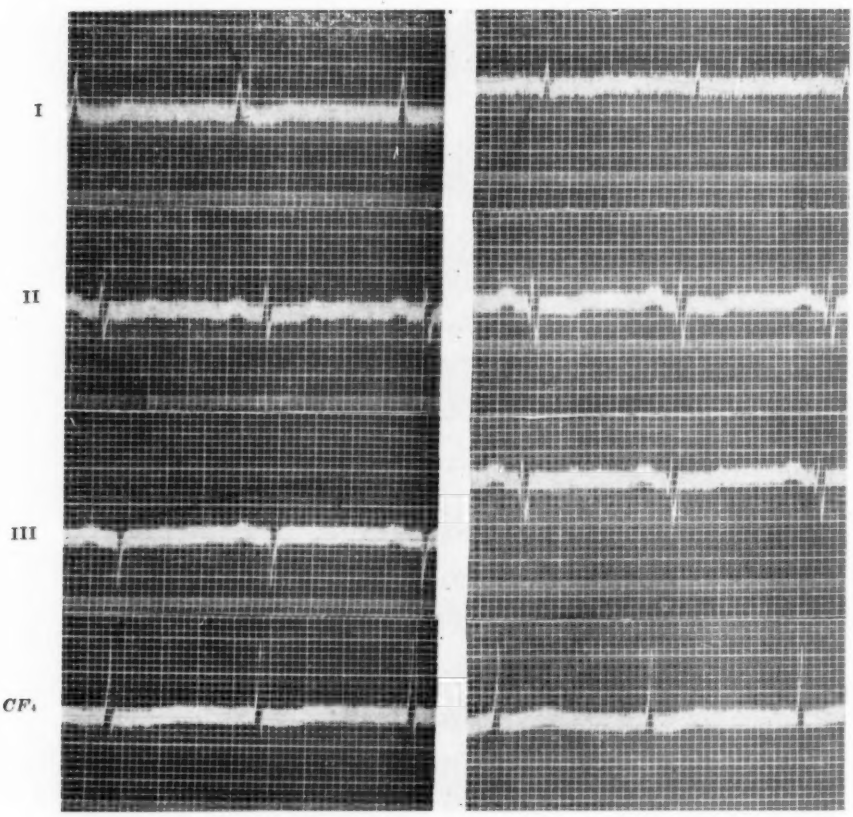


Fig. 4.—Sept. 10, 1941.

The last admission was on Sept. 30, 1940. The history, as given by his wife, was that he had suddenly slumped to the ground while talking to some friends, and that, after the fall, it had been noted that he had right-sided paralysis, with some speech impairment. On admission he was stuporous and acutely ill. Right-sided, flaccid paralysis was present. There were no gross abnormalities of the skull. The pupils were equal, circular, and regular in outline, and reacted readily to light and in accommodation. The ears, nose, and throat were essentially negative. Examination of the chest disclosed dullness at the bases of both lungs, with diminution of the breath sounds and slightly prolonged expiration. No râles were heard. Evidence of atelectasis was found roentgenologically; this disappeared subsequently. The blood pressure was 170/120, and the pulse rate was 106; the pulse was irregular, but there was no pulse deficit. The heart sounds were muffled and no murmurs were heard. There was no evidence of congestive failure. The remainder of the examination showed nothing remarkable. The diagnosis was infarction (embolic) of the left internal capsule, secondary to hypertensive and arteriosclerotic heart disease, with auricular fibrillation. The erythrocyte, leuco-

cyte, and differential leucocyte counts were normal. The serologic reactions were negative. Chemical examination of the urine and blood showed nothing abnormal. He remained in a semicomatose state for two days, but roused enough on the third to take nourishment and try to talk. Digitalis was then continued, depending upon the heart rate. The electrocardiogram (Fig. 3) still showed left axis deviation, evidence of myocardial damage, and auricular fibrillation. The patient improved so much that he could get about with assistance. On Sept. 10, 1941, it was noted that his pulse was regular, and synchronous with the apical beat. An electrocardiogram (Fig. 4) showed normal sinus rhythm. The rhythm has remained normal to date (Fig. 5). Subsequent electrocardiograms, not reproduced here, continued to show normal sinus rhythm.



A. *B.*

Fig. 5.—*A*, Oct. 3, 1941. *B*, Nov. 1, 1941.

DISCUSSION

Auricular fibrillation, from the time of its inception, may be either of two types, i.e., paroxysmal, which may last from several minutes to several days, and persistent or permanent, which tends to continue throughout life. The actual records in this case go back only five and one-half years, but the statement of the patient's personal physician suggests that he had had auricular fibrillation for eleven years. The

statement of the wife that the patient had a cardiac ailment fifteen years earlier is not conclusive, for there is no evidence as to the type and severity of the lesion that existed at that time. During three out of the four periods of hospitalization, clinically and electrocardiographically, auricular fibrillation was demonstrated. The return to normal sinus rhythm was corroborated by the electrocardiogram.

When it was discovered clinically that the heart was beating regularly, it was at first thought that the patient had complete auriculoventricular dissociation, in addition to auricular fibrillation. This occurs in some cases of auricular fibrillation during digitalis therapy. This was disproved by the electrocardiogram, which demonstrated the presence of P waves and their absolute regularity with reference to their corresponding QRS complexes. He did not receive digitalis in unusual doses, nor did he receive any quinidine. No unusual drug therapy was instituted at any time. The return to normal sinus rhythm was spontaneous.

CONCLUSIONS

A case in which long-standing auricular fibrillation was replaced by normal sinus rhythm is reported; only one other such case has been reported.

Electrocardiograms taken over a period of five and one-half years are shown, including tracings showing normal sinus rhythm.

The statement of the patient's personal physician indicated that the duration of fibrillation was eleven years.

The return to normal sinus mechanism was spontaneous.

REFERENCES

1. Burch, George E.: Fibrillation of Twenty-Two Months' Duration, With Return to Normal Sinus Mechanism Without the Aid of Quinidine, AM. HEART J. **18**: 102, 1939.
2. Bishop, L. F.: Fibrillation of Auricle Returned to Normal Rhythm, Am. J. M. Sc. **165**: 29, 1923.
3. Brill, I. C.: Auricular Fibrillation; the Present Status With a Review of the Literature, Ann. Int. Med. **10**: 1487, 1937.
4. Cowan, John, and Ritchie, T.: Diseases of the Heart, Baltimore, 1935, William Wood & Co.
5. Levine, Samuel A.: Clinical Heart Disease, Philadelphia, 1940, W. B. Saunders Co.
6. Pardee, Harold E. B.: Clinical Aspects of the Electrocardiogram, New York, 1941, Paul B. Hoeber, Inc.
7. Criteria Committee of New York Heart Association: Nomenclature and Criteria for Diagnoses of Diseases of the Heart, New York, 1940.
8. White, Paul D.: Heart Disease, New York, 1934, The Macmillan Company.
9. Fishberg, Arthur M.: Heart Failure, Philadelphia, 1940, Lea & Febiger.
10. Lewis, Sir Thomas: Clinical Disorders of the Heart Beat, London, 1933, Shaw & Sons, Ltd.
11. Stroud, William D.: The Diagnosis and Treatment of Cardiovascular Diseases. Vol. 1, Philadelphia, 1941, F. A. Davis Co.
12. Katz, Louis: Electrocardiography, Philadelphia, 1941, Lea & Febiger.
13. Bishop, L. F., and Bishop, L. F., Jr.: Auricular Fibrillation Observed for 25 Years, J. A. M. A. **114**: 955, 1940.

Abstracts and Reviews

Selected Abstracts

Murphy, Q.: The Influence of the Accelerator Nerves on the Basal Heart Rate of the Dog. Am. J. Physiol. **137**: 727, 1942.

Many investigators have believed that the cardio-accelerator nerve fibers are in a state of tonic activity. In twenty-four unanesthetized dogs without food for twelve hours and resting for sixty minutes, the basal heart rate or the lowest rate that could be obtained by training was found to range between 42 and 65 beats per minute. Bilateral removal of the stellate and upper five thoracic ganglia failed to result in an appreciable change in the basal heart rate. Under the conditions of these experiments, the accelerator nerves do not seem to be in tonic activity and the accelerator mechanism would seem to be an emergency mechanism.

ROTH.

Katz, L. N., Jochim, K., and Goldman, A.: The Effect of an Injured Area on the Electrical Field of the Heart Based on Experiments With Models. Am. J. Physiol. **137**: 779, 1942.

The electrical field was explored in models made to represent in simple form the syncytial cell of a normal heart and a heart with an injured, unresponsive area. In the "normal heart" model during electrical diastole the entire external or body field was found to be an equipotential region at the same potential as the external surface of the "polarized cell membrane," i.e., positive with respect to ground. During electrical systole when depolarization was complete the entire field was at ground potential.

In the "injured heart" model during electrical diastole the external field was still positive throughout with respect to ground; however, it was no longer an equipotential region because the "injured region" was only partially polarized. This led to the flow of the resting injury current. During electrical systole the potential distribution in the field was altered due to the deporalization of "uninjured" portions of the "cell membrane," while the "injured region," being unresponsive, retained its partial polarization. This gave rise to the activity injury current. It was shown with these models that distant points in the external field may experience large changes in potential with respect to ground between diastole and systole, and so cannot be considered to be indifferent. Further, the resting injury current and the activity injury current and hence the monophasic curve of injury can be explained in these models on the basis of the classical membrane theory. The activity injury current is shown to be due to the depolarization of uninjured regions and not to any process occurring within the injured area.

AUTHORS.

Hurwitz, M., and Friedberg, L.: Relationship of Heart Size to Cholesterol Content in Experimental Atheromatosis of the Rabbit. Arch. Path. **34**: 875, 1942.

Anatomically demonstrable sclerosis of the coronary arteries with resultant myocardial fibrosis was produced in rabbits by the feeding of diets high in cholesterol. A comparison of the heart weights of these rabbits with those of a control series

showed, as reported previously, that there is a distinct increase in the size and weight of the heart in the cholesterol-fed group and that this increase is reflected in the percentage of the total body weight comprised by the heart weight.

The hearts of the cholesterol-fed group were analyzed quantitatively for cholesterol and the results compared with those obtained in a control series. It was found that the cholesterol-fed animals showed a definite increase in the cholesterol content of the heart both in the free and in the esterized form. This increase, though unequivocal, could in no way account for the increased weight of the heart.

Since previous studies exclude the dynamic significance of lesions of the aortic valve, and since aortic sclerosis per se does not cause an increase in the work of the left ventricle, it is concluded that myocardial ischemia resulting from atherosclerosis of the coronary arteries per se can be the sole cause of cardiac hypertrophy.

AUTHORS.

Starr, I.: Abnormalities of the Amount of the Circulation (Hyper- and Hypokinemia) and Their Relation to Neurocirculatory Asthenia and Kindred Diagnoses. Am. J. M. Sc. **204**: 573, 1942.

The author's observations are that the great group of patients with symptoms referable to their circulations, but without disease demonstrated by the usual clinical tests, can be properly divided into three sub-groups depending on the condition of their resting circulations. In the hyper- and hypokinemic groups, and in a few patients of the normokinemic group, the author has demonstrated an abnormality of function which may well be the cause of many of their characteristic symptoms.

Patients with essential hypokinemia have resting circulations similar to those found in many cases of organic heart disease. Therefore it is not surprising that these two groups share many symptoms and that such a term as functional heart disease, which recognizes the similarity, has arisen. Certainly such symptoms as dyspnea on exertion, weakness, dizziness when upright, and susceptibility to fainting attacks, are consistent with the findings of subnormal circulation.

Patients with essential hyperkinemia share their circulatory abnormality with cases of hyperthyroidism, and it is not surprising that they have much the same appearance to gross inspection. Apparently the characteristic appearance of hyperthyroidism, so readily recognized at a glance by experienced clinicians, is more nearly related to the circulation than to the metabolic rate. Perhaps this is why patients with hyperthyroidism complicated by a cardiac disease which has reduced their circulation, may pass so long unrecognized. Without hyperkinemia the characteristic appearance is missing and the attending physician does not immediately see the need of an estimation of basal metabolic rate.

AUTHOR.

Hirsch, S.: Concerning the Finer Structure of the Circular Blood Vessels, Especially the Finding of Autonomic Stretches of Blood Vessels in the Human Heart. Cardiologia **6**: 105, 1942.

The main stem and the larger branches of the coronary artery are to be considered as an intermediate stage between elastic and muscular artery types. The gradual transition to the muscular type takes place in the medium arteries. The structure of the walls becomes more manifold as the caliber decreases; the special morphological functional circumstances of the supply region are here imprinted histologically. The research carried out under definite technical conditions permits the conclusion that autonomously functioning vessel stretches (glomus) are present in the heart wall, which serve to adjust the current acting on the vessel wall to the changing interstitial pressure of every heart phase (circulation derivative).

AUTHOR.

Evans, W., and Wright, G.: The Electrocardiogram in Friedreich Disease. Brit. Heart J. 4: 91, 1942.

The electrocardiogram in 38 patients with Friedreich disease was specially studied. This investigation has convinced us that the condition may sometimes be as much an affection of the heart as of the nervous system.

In only one patient, with Stokes-Adams disease, did clinical examination of the heart show any abnormality; in his case the pulse was slow from complete heart block and irregular from extrasystoles.

Cardioscopy, carried out in all except 4 bedridden patients, showed slight enlargement of the left ventricle in 8, and 5 of these had prominent cardiographic changes.

The cardiogram showed conspicuous or significant changes in 12 of the 38 patients. There were slight changes in another 10. In the remaining 16 the curve was physiological. In the first group 1 patient had complete heart block, 3 had a T_1 type of coronary curve, and 3 had a T_2 type of curve. In 5 the T wave was low and usually inverted in all three limb leads. In 5 of 10 patients showing lesser changes, the S wave was deep and slurred in lead I and usually in lead II, and similarly in leads II and III in the other 5 patients.

When the relation of abnormal signs in the nervous system to the cardiographic changes was examined, it was found that absence of tendon reflexes and extensor response of the plantar reflex were more common in patients with abnormal cardiograms. In respect of other nervous signs it may be said generally that they were more widespread in patients with the more conspicuous cardiographic changes. Of greater significance appeared to be the high incidence of a family history of Friedreich disease in those showing cardiographic changes. Thus 15 out of 22 patients with abnormal cardiograms (8 of them showing gross changes) had one or more relatives, usually a brother or a sister, similarly affected, while only 4 out of 16 patients with normal curves provided this family history. The affected members of the same family tended to show identical cardiographic changes.

The electrocardiogram may help to establish the diagnosis of Friedreich disease when the neurological manifestations are not altogether typical of the condition; an abnormal tracing lends support to the diagnosis, but a normal curve does not exclude it. In prognosis too the cardiogram can be of assistance; when it proves involvement of the bundle of His it may foretell auriculoventricular dissociation and Stokes-Adams disease with its ominous outlook. The exact significance of a "coronary type" of curve is not known yet, but it is probable that only such cases are prone to develop heart failure, although the proximity of this event may be more closely related to the degree of cardiac enlargement, which is best determined by cardioscopy.

For these reasons we would say that the investigation of a patient with Friedreich disease is incomplete without electrocardiography and cardioscopy.

AUTHORS.

Barber, H.: Electrocardiographic Changes Due to Trauma. Brit. Heart J. 4: 83, 1942.

A series of 33 hospital accident cases has been examined within two days of the injury. Patients with a severe blow over the chest or a crushing injury of the thorax were selected as opportunity arose.

Eight abnormal electrocardiograms were obtained. The changes observed are comparable with results obtained in animal experiments.

AUTHOR.

Kennedy, J. A.: A New Concept of the Cause of Patency of the Ductus Arteriosus. Am. J. M. Sc. 204: 570, 1942.

The cause of closure of the ductus arteriosus at birth is important to the knowledge of physiology and of heart disease.

The author's observations on guinea pigs show that the ductus is different from the other great arteries both histologically and in its physiologic reactions.

The ductus arteriosus during late fetal life is potentially an active structure and is able to close in response to certain definite stimuli.

It normally closes within the few minutes following birth and remains closed. If this normal process of closure is interrupted, patency of ductus arteriosus results. Thus, it may be the interruption of a normal physiologic process which causes this form of congenital heart disease when it occurs alone, not in some bizarre malformation.

AUTHOR.

Hansen, A. E.: Pleurisy With Effusion as a Manifestation of Rheumatic Fever. Journal-Lancet 62: 158, 1942.

Pleurisy with effusion characterized a rheumatic recrudescence in a 12-year-old boy who experienced a sudden onset of fever with slight dyspnea and pain in the chest several weeks following a typical attack of polyarthritis. Failure to isolate any organisms in the pleural fluid together with the rapid resorption of the exudate seemed to establish this as a clear-cut rheumatic pleurisy with effusion. This manifestation of rheumatic fever is discussed briefly in relation to other types of pleural effusion, and the protean symptomatology of the serious and all-too-prevalent disease of rheumatic fever is reviewed.

AUTHOR.

Gordon, W. H., Parker, F., Jr., and Weiss, S.: Gummatous Aortitis. Arch. Int. Med. 70: 396, 1942.

Three cases of macroscopic gummatous aortitis are reported. In Case 1 the gummatous process of the aorta completely occluded the right coronary artery and partially occluded the left one. In Case 2 gummatous lesions were present also at the base of the aortic valve. In Case 3 an extensive gummatous process affected not only the aorta but the pulmonary artery; the necrotic gummatous lesions resulted in perforation of the aorta into the trachea. In none of these three cases was there gumma in the myocardium.

Gummatous aortitis is mainly localized in the media, but usually the adventitia and the intima are also affected. Macroscopic gummatous aortitis is rare, and the number of authentic cases described in the recent literature, including the three described by us, totals less than ten. In addition to the case reported here of occlusion of the coronary arteries by gumma, only two cases of this condition were found in the literature.

Gummatous lesions of the aorta are responsible for symptoms only if they lead to narrowing or occlusion of the coronary arteries or to perforation of the aorta. Dyspnea, orthopnea, precordial distress, cardiac asthma, pulmonary edema and hemoptysis, when present, are referable to such lesions of the coronary arteries or the aorta.

Of three hundred and sixty cases of chronic syphilitic aortitis, microscopic gummas occurred in eight (1:45). This ratio must be considered minimal. Whether in all cases of chronic aortitis the lesions go through a stage of microscopic gummatous aortitis is not known.

In three of the three hundred and sixty cases of chronic syphilitic aortitis an acute abscesslike lesion was encountered. In a control group of two hundred and twenty-four cases similar "acute aortitis" occurred in six cases (in one associated with mediastinitis, in one with lymphatic leucemia and in four with medionecrosis idiopathica cystica). Chronic lesions of the aorta predispose to secondary acute abscesslike lesions.

The differential morphologic characteristics of gummatous aortitis, on the one hand, and those of acute bacterial aortitis, rheumatic aortitis, tuberculosis of the aorta, atherosclerotic necrosis, medionecrosis idiopathica cystica and aortitis of undetermined origin, on the other hand, are described.

In the group of three hundred and sixty cases of chronic syphilitic aortitis, atheromatous changes over the area affected by the syphiiitic lesions were prominent. This suggests that chronic syphilitic lesions of the aorta predispose to the development of local atherosclerosis.

AUTHORS.

Mahaim, I.: Benign Coelothelioma of Tawara's Node. Cardiologia 6: 57, 1942.

This is a description of a benign tumor, sui generis, of Tawara's node, of which only five observations are known, and which always provokes a heart block. The first time it was described by Mönckeberg under the name of "lymphangioendothelioma," but in fact it is a tumor of embryonic origin which develops from the epicardic coelothelial cells (Deckzellen).

AUTHOR.

Eichna, L. W., and Bordley, James, III. Capillary Blood Pressure in Man. Direct Measurements in the Digits of Normal and Hypertensive Subjects During Vasoconstriction and Vasodilatation Variously Induced. J. Clin. Investigation 21: 711, 1942.

The digital capillary blood pressure for all locations in the capillary varied within wide limits, and was qualitatively and quantitatively similar in both normal and hypertensive subjects. This maintained during the following observations which apply equally to both groups of subjects.

Such physiologic influences as neurogenic vasoconstrictions, reactive hyperemia, reflex vasodilatation, and variations in skin temperature between 27° C. and 35° C., all induced such comparatively small changes in the digital capillary blood pressure that the resultant values did not fall beyond "resting" limits. These changes were considerably smaller than the much larger alterations in digital blood flow known to occur under similar circumstances.

Only during increases in local venous pressure did the digital capillary blood pressure consistently exceed "resting" values.

Wide variations in digital capillary blood pressure persisted during reflex vasodilatation, a state during which digital circulation is considered to be full, standard, and reproducible.

During vasodilatation, induced reflexly or by locally injected histamine, there was a disproportionately greater increase in pressure in the venous limb than elsewhere in the capillary. The other states all influenced equally the digital capillary blood pressure in all locations of the capillary.

No correlation existed between the digital capillary blood pressure and the arterial pressure, except perhaps during the hyperemia induced by histamine.

Some mechanism maintains the digital capillary blood pressure within relatively fixed limits, even during marked changes in digital blood flow and arterial pressure.

The similarity of the digital capillary blood pressure of normal and hypertensive subjects indicates that in the digits the increased vascular resistance of hypertensive subjects is precapillary, presumably arteriolar. During the vasodilatation of reactive

hyperemia and reflex vasodilatation, the digital capillary blood pressure was essentially equal in both normal and hypertensive subjects; during vasodilatation induced by locally injected histamine, the capillary pressure to the hypertensive subjects exceeded that in normal subjects. These few experiments may suggest that in the digits histamine appeared to relax, at least to some extent, the increased vascular resistance of hypertension whereas reactive hyperemia and reflex vasodilatation did not.

These data and the conclusions derived therefrom apply only to the capillary blood pressure in the nail-folds of the fingers.

AUTHORS.

Eichna, L. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate. J. Clin. Investigation **21**: 731, 1942.

During the hypertension induced by paredrinol sulfate in subjects with normal arterial pressures, the digital capillary blood pressure remained within the limits previously established for the same individuals when their arterial pressures were normal.

This finding maintained equally for capillaries in digits with intact innervation and after preganglionic sympathectomy.

At the height of the paredrinol-induced hypertension, the vasodilatation of local reactive hyperemia did not significantly alter the digital capillary blood pressure. The hyperemia of the histamine-flare was usually associated with a rise in the digital capillary blood pressure to values which just exceeded the pressures obtained during the resting state at both normal and elevated arterial pressures.

AUTHOR.

Abell, R. G., and Page, I. H.: The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits. J. Exper. Med. **75**: 673, 1942.

Experimental renal hypertension in rabbits causes persistent, visible constriction to occur in the arterioles of the ears which is not great enough to restrict the flow of blood to the tissues but is sufficient to increase peripheral resistance. The constriction is due to the direct action of a substance on the arterioles since it occurs in the absence of nerves to vessels. It is associated with the appearance of new arteriovenous anatomoses. Since many of these phenomena have been reproduced by injection of angiotonin, this evidence is consonant with the view that the hypertension is due to angiotonin or some similar substance.

AUTHORS.

Schroeder, H. A.: "Essential" Hypertension. A Concept of Its Mechanism. Am. J. M. Sc. **204**: 734, 1942.

A way of thinking about arterial hypertension has been presented, which takes into account the possible role of renal ischemia and those factors which cause it.

AUTHOR.

Di Palma, Joseph R.: Quantitative Alterations in the Hyperemia Responses to Local Ischemia of the Smallest Blood Vessels of the Human Skin Following Systemic Anoxemia, Hypercapnia, Acidosis, and Alkalosis. J. Exper. Med. **76**: 401, 1942.

The responsiveness of the smallest blood vessels of the human skin was measured in systemic anoxemia, hypercapnia, acidosis, and alkalosis. A method was used which measured quantitatively the reactive hyperemia produced by a standardized

period of local ischemia of those fine vessels. By timing the clearing period of the threshold hyperemia response a direct indication of blood flow in these fine vessels was obtained. The following conclusions were reached concerning the responses of the smallest blood vessels of the skin.

Systemic anoxemia causes a decrease in sensitivity to local ischemia and a slowing of the blood flow.

Hypercapnia prevents the changes resulting from anoxemia.

These changes in the smallest blood vessels of the skin occur independently of changes in pulse rate, blood pressure, and respiratory rate and depth.

With systemic acidosis there is a decrease in sensitivity to local ischemia and a slowing of blood flow. The exact opposite takes place in systemic alkalosis.

The view is advanced, after due consideration of the facts, that the carbon dioxide concentration of the blood, or something directly associated with it, is the most important factor determining the sensitivity of these vessels, rather than oxygen saturation or changes in blood pH.

AUTHOR.

Peery, T. M.: Incomplete Rupture of the Aorta: A Heretofore Unrecognized Stage of Dissecting Aneurysm and a Cause of Cardiac Pain and Cardiac Murmurs. Arch. Int. Med. **70**: 689, 1942.

Incomplete rupture of the aorta is closely akin to dissecting aneurysm; it is the condition which exists after a tear has occurred in the vessel wall but before dissection has begun. It may, in the absence of dissection, cause pain in the chest and sudden dyspnea and is frequently associated with murmurs at the aortic area of the precordium. It is probably more frequent than dissecting aneurysm proper and may or may not be followed by dissecting aneurysm. If incomplete tear was recognized clinically dissection might be prevented in some cases by measures which tend to lower the blood pressure, thus permitting healing of the vessel wall.

The following suggestions may be of help in making an ante-mortem diagnosis of incomplete rupture of the aorta:

If the patient has been under observation for hypertension and returns complaining of sudden suffocation and dyspnea, with or without substernal pain, and if examination discloses either a systolic or a diastolic aortic murmur or both—murmurs which have not been present previously—incomplete aortic rupture should be strongly suspected. A harsh or rasping type of murmur would be particularly suggestive.

If the patient is seen for the first time during an acute attack, the diagnosis of incomplete rupture of the aorta would have to be made largely by exclusion. If no murmurs are detected, an incorrect diagnosis of coronary thrombosis may be made. If there is a diastolic murmur at the aortic area a diagnosis of syphilitic aortic valvulitis may be made, and the pain and suffocation may be assigned to narrowing of the coronary ostiums. The coincidence of hypertension and negative serologic reactions for syphilis may raise some doubt as to the correctness of this diagnosis. The suddenness of onset of symptoms may cause the diagnosis of ruptured aortic valve cusp to be considered. In dissecting aneurysm, which might also be confused with incomplete rupture, pain is usually more severe, and characteristically, the severity and the location of the pain change as dissection continues.

If the patient is seen for the first time because of heart failure due to aortic insufficiency, the correct diagnosis of incomplete aortic rupture would be extremely difficult. If the onset of symptoms of heart failure is sudden, if the patient shows marked hypertension and if clinical evidence of syphilitic and of rheumatic infection is lacking, it may occasionally be possible to make a correct diagnosis of incomplete aortic rupture as the cause of aortic insufficiency.

Careful search of the literature has failed to disclose an instance in which a correct diagnosis of incomplete rupture of the aorta has been made ante mortem.

AUTHOR.

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. VI. Pectin Atheromatosis and Thesaurosis in Rabbits and Dogs. Arch. Path. 34: 883, 1942.

Pectin solutions either freshly prepared and neutralized with phosphate buffer solution or autoclaved and neutralized were injected into dogs and rabbits.

The immediate effects produced on the blood by either of the two solutions are shown in colloidoclastic leucopenia, acceleration of erythrocytic sedimentation and moderate shortening of clotting time.

Repeated injections of pectin solutions do not cause any increase in the viscosity of the plasma or any changes in the number and the ratio of leucocytes.

In dogs and rabbits given injections of the freshly prepared pectin solution, marked foam-cellular storage phenomena develop in the spleen, liver, kidney and marrow in addition to foam-cellular atheromatosis of the various arteries. Older vascular lesions of this origin are characterized by hyaline intimal thickening with or without calcification and by hyaline necrosis and calcification in the media underneath.

Dogs and rabbits given injections of the autoclaved pectin solution showed, on the other hand, with the exception of one rabbit, only minor storage phenomena in the bone marrow and foci of hyaline degeneration and thickening of the arteries.

These differences in degree and type of reaction are due to the fact that pectin solutions are markedly depolymerized when exposed to heat and lose thereby much of their macromolecular characteristics and their original physicochemical properties.

These observations confirm the concept of the presence of a fundamental causal relation between physicochemical colloidal disturbances of the plasma and vascular atheromatosis and organic thesaurosis.

AUTHOR.

Logue, R. B.: Acute Cor Pulmonale. J. M. A. Georgia 31: 163, 1942.

Three case reports of massive pulmonary embolism have been presented, with the electrocardiographic changes which occurred in each. Minimal changes were present in one tracing, the typical McGinn-White type of change was present in another, and in the other serial electrocardiograms simulated those seen in posterior myocardial infarction.

AUTHOR.

Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy. Medicine 21: 269, 1942.

Symmetrical clubbing of the fingers and toes may be acquired in the course of various systemic diseases or may be hereditary. Unilateral and unidigital clubbing apparently occur in association with vascular and vasomotor diseases of the corresponding extremity or finger. Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of the extremities and may develop in any condition capable of producing clubbing.

Characteristic clinical and roentgenological changes occur in clubbing and hypertrophic osteoarthropathy.

Clubbing and hypertrophic osteoarthropathy are seen pathologically to consist chiefly of tissue hypertrophy and hyperplasia. In the original bone, however, osteoclasis and bone resorption may be stimulated.

Hypertrophic osteoarthropathy was produced experimentally in the dog by anastomosis of the pulmonary artery to the left auricle. The most significant circulatory change found was an increase in systemic cardiac output.

Clinical physiological observations have demonstrated in simple acquired symmetrical clubbing an increase in blood flow per unit of tissue caused chiefly by an increased digital arterial pressure. In hereditary clubbing and in hypertrophic osteoarthropathy these changes in digital arterial pressure and blood flow were absent. In unilateral clubbing they were variable.

Previous theories on the pathogenesis of clubbing are reviewed historically and discussed critically.

It is believed that increased peripheral blood flow will form a corner-stone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy.

AUTHOR.

Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. Am. J. Roentgenol. **48**: 141, 1942.

The diagnosis of dextrocardia with complete or partial transposition of viscera presents no diagnostic difficulties. However, it may be very difficult to differentiate the type of isolated dextrocardia in which there is inversion of the cardiac chambers from that type with a normal arrangement of the chambers. A method of differentiating this type during life is afforded by angiocardiography. The embryology of dextrocardia is discussed and three cases studied by angiocardiography are reported.

WILLIAMS.

Taylor, H. K., and Shulman, I.: Cardio-angiography. Radiology **39**: 323, 1942.

Fifteen patients were studied by electrocardiography, the stethogram, venous pressure determinations, circulation tests, kymography, teleroentgenography, and the relatively new method of cardio-angiography. Cardio-angiography visualizes the position of the various components of the heart, and it has been found that their positions are not entirely as described in textbooks. The information obtained from cardio-angiography with respect to the different components of the heart cannot be made available by any one or any combination of the routine methods of cardiac examination. The patients reported included two cases of mild congestive failure, hypertensives, one with renal insufficiency and nitrogenous retention, hypertension with bundle branch block, and a case of coronary occlusion. No serious or untoward reactions occurred. This type of cardiac examination is not recommended in patients who are debilitated, acutely ill, in severe cardiac decompensation, or in those having respiratory distress.

WILLIAMS.

Harrison, J. H.: The Indications and Limitations of Prostatic Surgery in the Presence of Cardiac Disease. Am. J. M. Sc. **204**: 469, 1942.

It is now generally agreed that patients having cardiac lesions often tolerate operation unexpectedly well. Indeed, the condition of the circulatory system usually improves immediately on relief of the obstructed bladder. The patient past middle life is not to be considered a poor operative risk for surgery of the prostate merely because of his years. For these reasons a proper evaluation of the factors involved when cardiac disease and urinary obstruction of prostatic origin coexist, is very important.

A careful history is most important in eliciting evidence of heart disease. Studies of exercise tolerance and vital capacity are of value in estimating the operative risk

of elderly patients. The patient who has recently been able to lead an active life is a good operative risk in spite of the presence of heart disease. Acute urinary retention precipitated by an acute cardiac crisis does not always require subsequent prostatectomy. By careful judicious management it is often possible to tide such patients over by conservative means until cardiac decompensation has cleared and normal micturition been resumed.

The patient who tends toward recurrent cardiac decompensation with associated urinary difficulties, has progressively more severe urinary retention with each successive cardiac breakdown. Several weeks should elapse after a coronary accident before resorting to surgery. In general the prognosis is better for these patients who have more than four weeks preoperative preparation, but this period must be judged on the basis of the merits of the individual case.

It is now more often a choice of the proper time to operate and the kind of operation to be employed rather than a decision for or against surgery, because modern methods do not impose a burden on even the diseased heart sufficient to upset its physiologic function when adequate medical care is given. After prostatectomy great improvement is manifested in the cardiovascular condition of the patient who has had urinary retention and heart disease. The operative approach and anesthesia depend on the characteristics and abilities of the patient, surgeon and anesthetist. In this clinic, the transurethral and perineal approaches have been used in recent years almost entirely, except when there is a definite and special indication for the suprapubic operation. The anesthesia of choice has been low spinal or ether.

AUTHOR.

Caviness, V. S., Umphlet, T. L., and Royster, C. L.: Blood Pressure and Sulfocyanates (Thiocyanate). Am. J. M. Sc. **204**: 688, 1942.

Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance. The concentration is approximately 50,000 times that of nitrites.

Each individual has a fixed constant blood sulfocyanate level.

Blood sulfocyanate concentrations tend to vary inversely with the blood pressure level, whether naturally or under treatment.

There appears to be normally in the body a balance between pressor substances and sulfocyanates. There is a definite tendency for low blood sulfocyanate levels to be associated with hypertension. Higher concentrations of blood sulfocyanates are not associated with hypertension.

Potassium sulfocyanate is a safe depressor substance if used properly; it lowers the diastolic pressure as well as the systolic.

The earlier in the course of the disease that treatment is instituted, the better the results that can be anticipated.

The lower the effective blood sulfocyanate concentration can be kept during treatment, the better the results will be.

The results of this work show such a strong rationale for the use of sulfocyanates in hypertension that the use need no longer be regarded as empirical.

AUTHORS.

Pelner, L.: The Effect of Ascorbic Acid (Vitamin C) on the Sensitivity to Salicylates in a Case of Rheumatic Fever. J. Lab. & Clin. Med. **28**: 28, 1942.

A severe case of rheumatic carditis became intolerant to sodium salicylate early in the course of the illness.

A low plasma ascorbic acid content, positive tourniquet test, and severe nosebleed suggested the presence of vitamin C deficiency.

The preceding diet of this patient proved to be deficient in vitamin C.

After the vitamin C intake was increased, sodium salicylate was again given in large amounts with impunity.

AUTHOR.

Burstein, J., Brown, G., and Klein, C.: Treatment of Congestive Heart Failure in Ambulatory Patients With an Orally Administered Mercurial Diuretic. J. Lab. & Clin. Med. **28**: 147, 1942.

Nine patients in congestive heart failure, attending an out-patient cardiac clinic, who were known to be well controlled by administration of intravenous mercurial diuretics, were given instead, an oral preparation of mercurial diuretic in a study to determine the usefulness of this medication in ambulatory patients. Seven of the nine patients (77.7 per cent) showed an increase in urinary output after taking this preparation, as compared with their output when no mercurial diuretic was given. In no case was the increase in urinary output as great as that resulting when the usual dose of a standard mercurial diuretic was given intravenously. Side reactions, chiefly cramps and diarrhea, occurred in six of the nine patients (66.7 per cent) and necessitated discontinuance of administration of the oral mercurial preparation.

AUTHORS.

Lamport, H.: The Effects on Renal Resistance to Blood Flow of Renin, Angiotonin, Pitressin and Atropine, Hypertension, and Toxemia of Pregnancy. J. Clin. Investigation **21**: 685, 1942.

Pitressin caused no consistent change in glomerular intra-capillary pressure, total effective renal arteriolar resistance, or in the afferent-to-efferent arteriolar resistance ratio in unanesthetized dogs.

Atropine added to pitressin increased total effective arteriolar renal resistance, with afferent arteriolar constriction predominating, in unanesthetized dogs.

Renin infused into unanesthetized dogs increased glomerular intracapillary pressure and total arteriolar resistance with neither afferent nor efferent constriction predominating consistently.

Angiotonin acted rather similarly to renin, but conclusions concerning it are subject to some doubt.

In one test on a human subject, angiotonin caused constriction of both sets of arterioles with afferent constriction predominating.

Afferent arteriolar constriction outweighed efferent constriction more than is normal in all of the seventeen cases of essential hypertension studied.

It is likely that the resistance of the afferent arterioles varies with blood pressure changes so as to preserve renal function.

A specific renal effect is the probable cause of the low filtration fraction seen in late severe toxemia of pregnancy. There is inadequate evidence to decide how much of this effect is primarily constriction of the efferent arterioles and how much, if any, is change in the permeability of the glomerular membrane to water and/or inulin and other sugars.

AUTHOR.

Rosenbaum, J. D.: The Influence of Alterations in Acid-Base Balance Upon Transfers of Carbon Dioxide and Bicarbonate in Man. J. Clin. Investigation **21**: 735, 1942.

The influence of changes in acid-base equilibrium upon the output of carbon dioxide by the lungs was studied in human subjects.

Overventilation produced large increments in respiratory output of CO_2. A portion of the CO_2 was given up by the tissues.

Ventilation with a CO_2-enriched air caused a marked diminution in the volume of CO_2 given out by the lungs. Part of the CO_2 retention was intracellular.

Alterations of the CO_2 content of blood, produced by ingestion of ammonium chloride, may be unassociated with any significant change in the output of carbon dioxide by the lungs.

The volume of distribution of bicarbonate ion administered intravenously as sodium bicarbonate was found to approximate the extracellular fluid volume as determined by the thiocyanate method.

AUTHOR.

Orgain, E. S., and Poston, M. A.: Sulfonamide Compounds in Therapy of Bacterial Endocarditis: A Comparison of the In Vitro Inhibitory Effects and the Bacteriostatic Activity. Arch. Int. Med. **70**: 777, 1942.

The in vitro inhibitory effects of seven sulfonamide compounds on twenty organisms isolated from seventeen patients suffering from bacterial endocarditis have been correlated with the clinical bacteriostatic activity of these drugs in a series of thirty-three clinical (in vivo) experiments.

A certain degree of correlation was found to exist between the in vitro inhibitory effects of these drugs and their clinical bacteriostatic activity.

The importance of preliminary in vitro experiments to determine the most effective drug and its possible clinical level of inhibitory action is emphasized.

AUTHORS.

Schill, E.: Auricular Flutter Appearing in the Course of a Protracted Treatment With Digitalis. Cardiologia **6**: 165, 1942.

Description is given of a case in which after a 20-day Verodigen-treatment and direct 8-day intensive treatment with digitalis (pulvis) a temporary attack of arrhythmia perpetua occurred.

AUTHOR.

To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

THE C. V. MOSBY CO., PUBLISHERS.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.
DR. ARLIE R. BARNES	Rochester, Minn.
DR. CLARENCE DE LA CHAPELLE	New York City
DR. NORMAN E. FREEMAN	Philadelphia
*DR. TINSLEY R. HARRISON	Winston-Salem
DR. GEORGE R. HERRMANN	Galveston
DR. T. DUCKETT JONES	Boston
DR. LOUIS N. KATZ	Chicago
*DR. SAMUEL LEVINE	Boston
DR. GILBERT MARQUARDT	Chicago
*DR. H. M. MARVIN	New Haven
*DR. EDWIN P. MAYNARD, JR.	Brooklyn
*DR. THOMAS M. McMILLAN	Philadelphia
DR. JONATHAN MEAKINS	Mon'real
DR. E. STERLING NICHOL	Miami
DR. FRANKLIN R. NUZUM	Santa Barbara
DR. HAROLD E. B. PARDEE	New York City
DR. WILLIAM B. PORTER	Richmond, Va.
*DR. JOHN SAMPSON	San Francisco
*DR. ROY W. SCOTT	Cleveland
DR. FRED M. SMITH	Iowa City
DR. HOWARD B. SPRAGUE	Boston
DR. GEORGE F. STRONG	Vancouver, B. C., Can.
DR. WILLIAM D. STROUD	Philadelphia
DR. HARRY E. UNGERLEIDER	New York City
*DR. HOWARD F. WEST	Los Angeles
DR. PAUL D. WHITE	Boston
DR. FRANK N. WILSON	Ann Arbor
*DR. IRVING S. WRIGHT	New York City
DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*